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Syracuse University

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Abstract

Reactions with 2-methylenetetrahydropyrans are underutilized in the literature, especially with respect to general methods demonstrating their nucleophilic nature. This work provides three general methods toward the synthesis of 2- β -oxygenated pyranyl substrates, which are key structural components of many biologically active polyketides and natural products.

The use of exocyclic enol ethers as nucleophiles was first demonstrated as a general process in three-component coupling reactions with secondary nucleophiles. The 2- β -hydroxy tetrahydropyran products were obtained in good to excellent yields through promotion with stoichiometric levels of titanium(IV) chloride at reduced temperatures. Only activated aldehydes or ketones worked as efficient coupling partners for this method. The point at which the secondary nucleophile was added to the reaction in progress was governed by the level of electrophile activation and in turn the amount of oxonium ion present for immediate capture. NOE studies determined that *cis*-tetrahydropyran products are solely formed with C₆-substituted enol ether substrates.

The carbonyl-ene reaction of exocyclic enol ethers provides 2- β -hydroxy dihydropyrans in excellent yields at room temperature. This process only requires catalytic levels of zinc chloride, and both activated and non-activated carbonyl-enophiles act as appropriate coupling partners. These mild reaction conditions produce dihydropyranyl substrates, which are equipped for further functionalization through the newly formed olefin. 2-Methylenetetrahydropyrans, bearing either mono- or di-substitution about the tetrahydropyran ring, were synthesized to determine if any chiral influence could be channeled to the dihydropyranyl products. The diastereomeric ratios of resulting products showed that exocyclic enol ethers with C₃ mono-

substitution or 2-methylenetetrahydropyrans with di-substitution, where at least one group is held axial, produced moderate levels of selectivity. Alternatively, the other substrates studied in this project demonstrated only low levels of chirality induction.

The carbonyl-ene reaction of exocyclic enol ethers has been applied bi-directionally to iodomethyl-2-methylenetetrahydropyrans to provide bis- β -hydroxypyrans. Good to excellent yields were obtained for the initial carbonyl-ene coupling and subsequent iodine elimination. The second carbonyl-ene coupling of 2-methylenedihydropyran was only effected with highly activated enophile components with zinc(II) chloride as the promoter. This reaction with ethyl glyoxylate proceeded in good to excellent yield with catalytic zinc(II) chloride. Only moderate yields of the pyranyl products were obtained with *p*-nitrobenzaldehyde and equimolar levels of zinc chloride. The bis- β -hydroxypyran products manufactured from this process are theoretically furnished for further functionalization into trioxadispiroketal systems. Attempted cyclization of these substrates under a number of acidic conditions failed to provide the desired bis-spiroketal systems. Therefore a step-wise approach to their manufacture was attempted, although this too failed to produce the bis-spirocyclic system due to difficulties experienced with iodide elimination.

NUCLEOPHILIC CARBON-CARBON BOND-FORMING REACTIONS OF 2-
METHYLENETETRAHYDROPYRANS

by

Laura Bateman

B.S., State University of New York at Oswego, 2005
M.S., Syracuse University, 2007

DISSERTATION

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List of Abbreviations

Ac	Acetyl
AIBN	Azobis(isobutyronitrile)
BBN	Borabicyclo[3.3.1]nonane
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	<i>t</i> -Butyloxycarbonyl
BPS	<i>t</i> -Butyldiphenylsilyl
Bz	Benzoyl
Cbz	Carbobenzyloxy
Cp	Cyclopentadienyl
CSA	Camphorsulfonic Acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DET	Diethyl Tartrate
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHP	Dihydropyranyl
(DHQ) ₂ AQN	Bis-Dihydroquinone Anthra-1,4-quinone
(DHQ) ₂ PHAL	Bis-Dihydroquinone 1,4-Phthalazinediyl Diether
DIBAL	Diisobutylaluminum Hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethylsulfoxide
dppe	(diphos) 1,2-Bis(diphenylphosphino)ethane
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDTA	Ethylenediaminetetraacetic Acid
EOM	Ethoxymethyl

HMPA	Hexamethylenetetraamine
Im	Imidazole
IPC	Isopinocampheyl
LBDD	Lithium p,p'-di-t-butylbiphenylide
LDA	Lithium Diisopropylamine
mCPBA	<i>m</i> -Chloroperoxybenzoic acid
MEM	β -Methoxyethoxymethyl
MOM	Methoxymethyl
MPM	<i>p</i> -Methoxybenzyl
Ms	Methanesulfonyl
NaHMDS	Sodium Dexamethyldisilazide
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide
NHC	N-Heterocyclic Carbene
NMO	N-Methylmorpholine-N-oxide
NOE	Nuclear Overhauser Effect
PCC	Pyridinium chlorochromate
PhthN	Phthalimido
Piv	Pivaloyl
PMB	<i>p</i> -Methoxybenzyl
PPTS	Pyridinium <i>p</i> -Toluenesulfonate
pTol	<i>p</i> -Toluene
pTsOH	<i>p</i> -Toluenesulfonic Acid
Pyr	Pyridine
Red-Al [®]	Sodium Bis(2-Methoxyethoxy)aluminum Hydride
SPHOS	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	Tetra-N-butylammonium fluoride
TBDPS	tert-Butyldiphenylsilyl

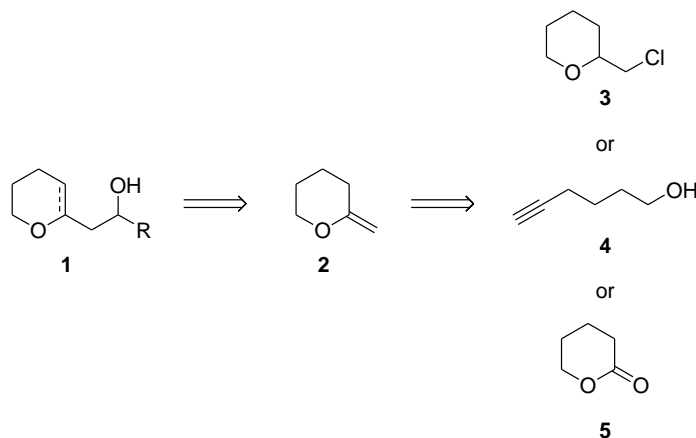
TBME	<i>t</i> -Butylmethylether
TBS	<i>t</i> -Butyldimethylsilyl
TES	Triethylsilyl
Tf	Triflate
TFA	Trifluoroacetic Acid
TFAA	Trifluoroacetic Anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TIPS	Triisopropylsilyl
TMEDA	N,N,N',N'-Tetramethylethylenediamine
TMS	Trimethylsilyl
TPAP	Tetra-N-propylammonium Perruthenate

Chapter 1. The Synthesis and Reactivity of 2-Methylenetetrahydropyrans

1.1 Overview

β -Hydroxytetrahydropyrans and their derivatives are present in a number of biologically active natural products. Organic synthesis is used to manufacture natural products, because often these molecules are not isolated from nature in reasonable yields. Therefore the synthesis of tetrahydropyrans is of importance to the synthetic organic community and beyond. β -Hydroxytetrahydropyran functionalities like **1** can be accessed through reactions of 2-methylenetetrahydropyrans (**2**). These exocyclic enol ethers can be synthesized by one of several methods (Scheme 1.1).

Scheme 1.1



This chapter will examine the different methods of exocyclic enol ether synthesis, which includes the elimination of alkyl halides (**3**), cyclization of acetylenic alcohols (**4**), and direct methylenation and alkylidenation of the corresponding lactone (**5**). Secondly, the reactivity of exocyclic enol ethers is addressed. Exocyclic enol ethers have been reported to undergo a number of processes, including their use as substrates in addition reactions, rearrangements, pericyclic reactions, and radical reactions, and their use as electrophiles and nucleophiles. The reactions of greatest significance in organic chemistry are those involving new carbon-carbon bonding.

Therefore, the primary focus will be on these transformations and the use of exocyclic enol ethers as nucleophiles.

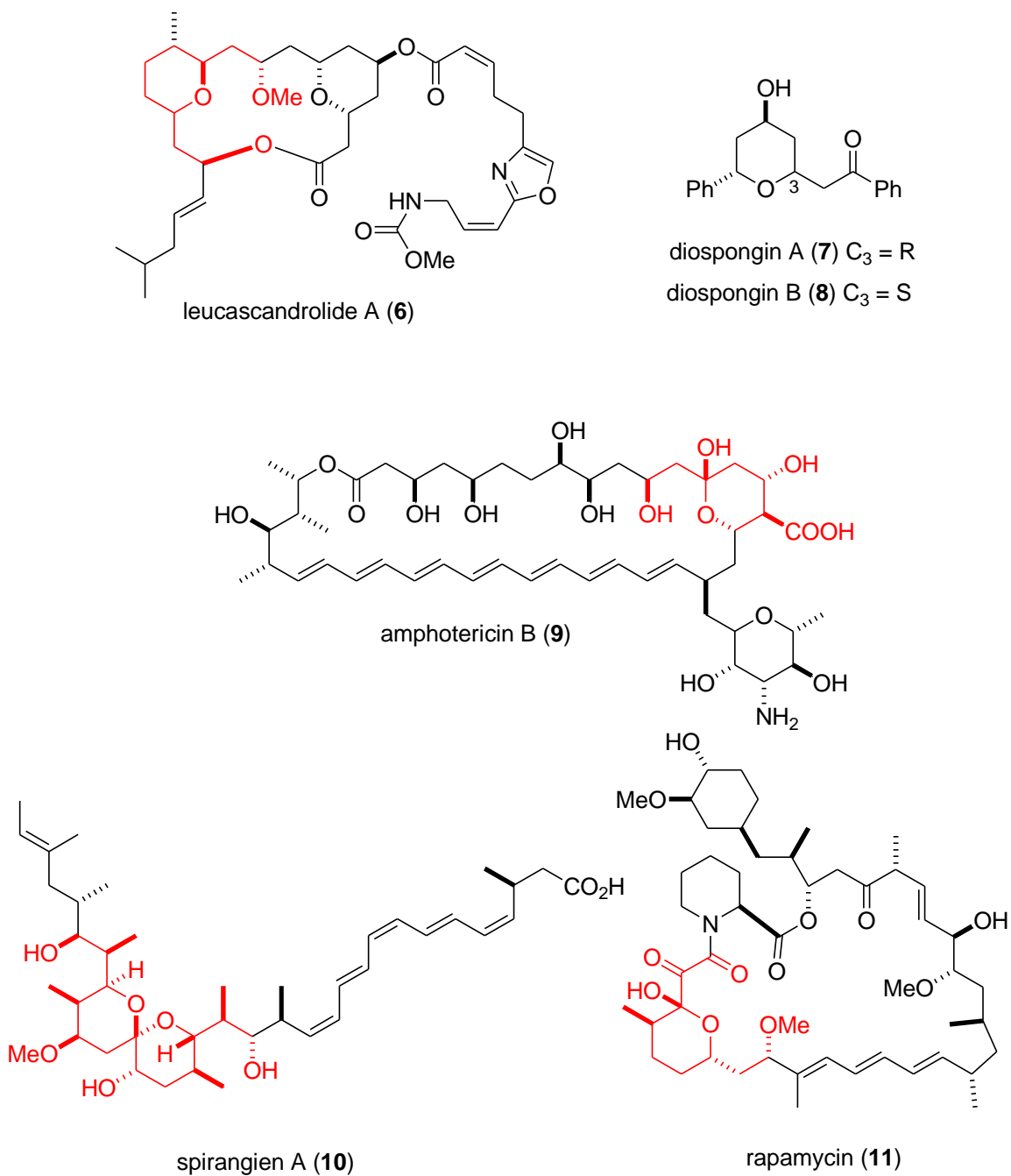
1.2 Background and Significance

β -Hydroxytetrahydropyrans and their derivatives are common moieties found in many natural products. These natural products are of synthetic interest because of their varied biological activities, which makes them effective drugs or worthy drug candidates. There are a number of interesting tetrahydropyranyl ketide derivative-containing natural products, which include, but are not limited to popular synthetic targets such as leucascandrolide A (**6**),¹ diospongin A (**7**) and B (**8**),² amphotericin B (**9**),³ spiroketal-containing natural product spirangian A (**10**)⁴ and rapamycin (**11**)⁵ (Figure 1.1).

Leucascandrolide A (**6**) contains within it a *cis*-1,6-substituted tetrahydropyranyl diketide. This natural product has a remarkable set of biologically active properties, making it a potential drug candidate. Leucascandrolide A shows marked cytotoxicity against human KB tumor cell lines and P388 leukemia cell lines, displaying IC₅₀ values of 0.05 and 0.25 μ g/mL respectively. Leucascandrolide A also shows antifungal inhibition against *Candida albicans*, a pathogenic yeast that attacks immune-compromised individuals including AIDs patients.⁶ The natural product is theorized to inhibit the cytochrome bc1 complex, which is used by cells to make ATP, an important source of a cell's energy. Blocking ATP formation triggers the cell to undergo apoptosis and eventually die.⁷

Leucascandrolide A was isolated in 1996 from the calcareous sponge *Leucascandra caveolata*, however attempts at re-isolation were unsuccessful.⁸ The natural product is believed to originate from a microbial colony present on the sponge rather than the sponge itself.

Figure 1.1



The high biological activity of leucascandrolide A, coupled with the inability to re-isolate the natural product, has led to a variety of synthetic approaches.⁹

Diospongin A (**7**) and B (**8**) are simple examples of tetrahydropyranyl ketide-containing natural products that differ only in the stereochemistry at the C₃ position of the tetrahydropyranyl ring. Both natural products were isolated from *Dioscorea spongiosa* in 2004,¹⁰ and since then a number of syntheses have been reported.¹¹ Diaspongin B has displayed anti-osteoporotic activity similar to the clinically used drug elcitionin.¹² Interest in the diospongins stems from the observed bioactivity and their relatively simple structure. Since diospongin is not an overwhelmingly complex molecule, it can be synthesized in a minimal number of steps. This makes diospongin B a synthetic target of possible pharmacological use, since fewer synthetic steps would reduce production costs and consequently cost to consumers.

Amphotericin B (**9**) was isolated from *Streptomyces nodosus* and is used as an antifungal and antiprotazoal agent.¹³ Oral preparations of this drug have been used to treat thrush, and it is also administered intravenously as a last resort to treat systematic fungal infections (cryptococcal meningitis) and parasitic protozoan infections (leishmaniasis and amoebic meningoencephalitis).¹⁴ Additionally, inoculation of amphotericin B to tissue cultures prevents fungal contamination. Amphotericin B causes cell death by associating with ergosterol, a component of the cellular membrane, forming trans-membrane channels that cause monovalent ion leakage. Because mammalian membranes contain similar sterols, toxicity can occur in amphotericin-treated patients.¹⁵ Thus Amphotericin is used as a last resort in critically ill patients. The structure of amphotericin B was fully established via X-ray crystallographic analysis,¹⁶ and both the total synthesis¹⁷ and biosynthesis¹⁸ of this molecule have been reported.

Spirangien A (**6**) is another example of a tetrahydropyranyl spiroketal-containing natural product of recent interest that was isolated from the *Sorangium cellulosum* strain of myxobacteria.¹⁹ Spirangien A exhibits both antifungal and cytotoxic biological activities, with

IC₅₀ values of 1.0×10^{-9} M against a L929 mouse fibroblast cell line.²⁰ This level of cytotoxicity is comparable to the popular anticancer drug Taxol,[®] which also exhibits nanomolar cytotoxicity against human cancer lines.²¹ Hence, spirangien A is a potential drug target for cancer treatment. To date, the mechanism of action that gives rise to the promising anticancer activity has not yet been determined. Total syntheses have been published by the Paterson²² and Ley²³ groups.

Rapamycin (**5**), also known as sirolimus, is a tetrahydropyranyl polyketide-containing natural product that is used in treatment of a multitude of diseases. Within this macrolide there exists a *cis*-tetrahydropyranyl ketide unit. This natural product was isolated from the bacterium *Streptomyces hygroscopicus*, which was found in a soil sample local to Easter Island in 1975.²⁴ Originally developed as an antifungal treatment, rapamycin is currently marketed by Wyeth (Rapamune) as a highly effective immunosuppressant amongst other uses. The drug is biosynthesized through the use of polyketide synthase and additional enzyme modifications.²⁵

Although quite similar in structure to tacrolimus, a tetrahydropyranyl ketide-containing, immunosuppressive, calcineurin-inhibiting drug,²⁶ rapamycin works by a different mode of action. Rapamycin binds to the cytosolic protein, FK-binding protein 12 (FKBP12), and inhibits the mammalian target of rapamycin (mTOR) pathway by directly binding to mTOR complex 1. Thus rapamycin inhibits the response to interleukin-2 and blocks the activation of T and B-cells.²⁷

The use of rapamycin as an immunosuppressant is preferred over other drugs because lower toxicities to the liver are observed.²⁸ Alternatively, internal use of tacrolimus has led to impaired kidney function and even chronic renal failure in patients. This makes rapamycin an especially effective drug for preventing organ rejection in kidney transplantations.

Not only is rapamycin a great drug candidate for immunosuppressive therapy, but it has also found use in a number of other treatments. Rapamycin has been found to exhibit antiproliferative properties and has been used in conjunction with coronary stents to prevent restenosis in coronary arteries following balloon angioplasty. This natural product is marketed as a sirolimus-eluting coronary stent (Cypher) by Cordis, a sub-division of Johnson and Johnson.

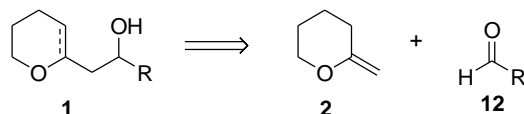
In studies of patients with tuberous sclerosis complex (TSC), a disease marked by benign tumor growth in various organs, inhibitory effects were observed, diminishing the reoccurrence of tumor formation in these patients. As part of this study researchers also discovered that symptoms of attention deficit hyperactive disorder (ADHD) and autism decreased. In fact autistic mice treated with rapamycin demonstrated marked increases in intellect within three days.²⁹ A treatment for autism would be especially valuable, with no current available treatment.

Additional studies have shown rapamycin to be an effective treatment toward autosomal dominant polycystic kidney disease,³⁰ decreasing cancer risk in patients with renal failure,³¹ and inhibiting HIV replication via downregulation of coreceptor CCR5³² and inhibition of the induction of autophagy.³³ Rapamycin's demonstrated bioactivity against a wide variety of high-impact diseases and disorders is convincing evidence that tetrahydropyranyl ketide-containing natural products are of value to the world.

These natural products are a small selection of biologically active tetrahydropyranyl-containing synthetic targets that attract interest. Not only are these tetrahydropyranyl ketides and derivatives interesting synthetic targets, but they also are prepared for use in the medical field. Our interest in these functional groups stems from the desire to showcase the nucleophilic nature of neutral exocyclic enol ethers. The approach focuses on utilizing 2-methylenetetrahydropyrans (**2**) as synthetic precursors (Scheme 1.2). The combination of these

exocyclic enol ethers with aldehydes under Lewis acid conditions yields tetrahydropyran **1**. This approach provides a highly convergent synthetic approach toward these tetrahydropyranyl moieties. We expect a broad application of our methodology to synthetic organic chemistry based on the varied interest in synthesizing tetrahydropyranyl ketide subunits.

Scheme 1.2

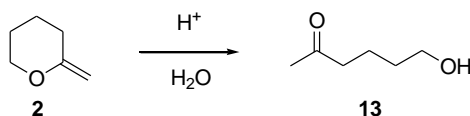


Exocyclic enol ethers have been underutilized in synthetic organic transformations, especially as nucleophiles. The limited study of these exocyclic enol ether substrates is possibly due to the tendency of these systems to undergo isomerization and hydrolysis in the presence of trace acid or heat.³⁴ These substrates, however, can be manufactured and successfully applied in organic transformations. In fact the manufacture and use of these substrates has sparked some interest in the field and has lead to the publication of two review articles.³⁵ The synthesis and subsequent chemistry of exocyclic enol ethers is discussed herein.

1.3 Synthesis of Exocyclic Enol Ethers

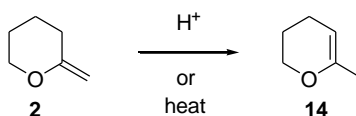
The synthesis of 2-methylene tetrahydropyrans has been achieved using several different strategies: two-step addition/elimination processes, cyclization of alkynyl alcohols, and direct methylenation of the corresponding lactone. In all cases their synthesis is not trivial. The synthesis and subsequent chemistry of exocyclic enol ethers is complicated by their possible hydrolysis (Scheme 1.3),³⁶ and the propensity of these systems to undergo isomerization to the

Scheme 1.3



endocyclic isomer, dihydropyran **14**, in the presence of trace acid or excessive heat (Scheme 1.4).³⁷ Use of appropriate reaction conditions and proper handling, however, makes these moieties accessible through a number of reactions.

Scheme 1.4

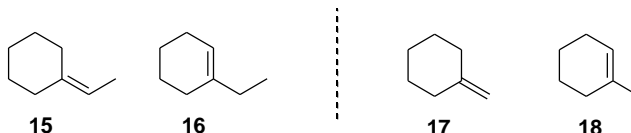


2-Methylenetetrahydropyran **2** can isomerize to dihydropyran **14** with trace acid or heat because the later heterocycle is stabilized by three factors: increased hyperconjugative effects,³⁸ decreased steric repulsions,³⁹ and increases in favorable orbital overlap between the ring oxygen and pi electrons.⁴⁰ The transition from exocyclic enol ether **2** to endocyclic enol ether **14** involves an increase in olefin substitution. The increase in substitution is associated with greater hyperconjugative effects, which stabilize the olefin through delocalization of alkyl bonding electrons with the double bond pi electrons.⁴¹ Isomerization studies of the corresponding carbocycles, however, indicates that the stability of endocyclic over exocyclic olefins involves more than just hyperconjugative effects.

The heats of hydrogenation for ethylenecyclohexane (**15**) and ethyl cyclohexenes (**16**) were compared (Figure 1.2).⁴² In this system the exo and endo olefins possess similar conjugative effects due to equivalent substitution, but an energy gap between the isomers still exists, favoring the endocyclic double bond. The energy difference between isomers **15** and **16** is 1.2 Kcal/mol, favoring the endocyclic olefin, as opposed to 2.4 Kcal/mol for the corresponding methylene/methyl derivatives (**17** and **18**) where the degree of hyperconjugation differs. The energy values for the carbocycles can be related to the corresponding heterocyclic olefins **2** and **14**. In fact studies have shown exocyclic enol ether **2** is stabilized (4.3 kJ/mol) when a methyl

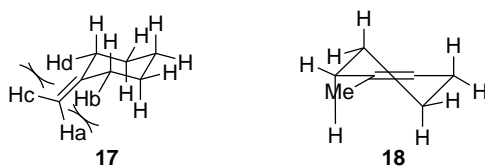
group is attached to the exocyclic olefin like the stabilization seen for (Z)-ethylidenetetrahydropyran.⁴⁰ Nonetheless, an energy difference still exists between isomers **15** and **16** and indicates that stabilizing effects beyond hyperconjugation are responsible for thermodynamically-favored endocyclic enol ether formation.

Figure 1.2



Steric factors also contribute to energy differences between exo and endo isomers. Methylene cyclohexane **17** experiences steric repulsion between equatorial hydrogens (Hb and Hd) and hydrogens Ha and Hc of the exocyclic methylene unit respectively (Figure 1.3).⁴³ These non-bonding interactions are not present in the endocyclic system **18**. Between hyperconjug

Figure 1.3

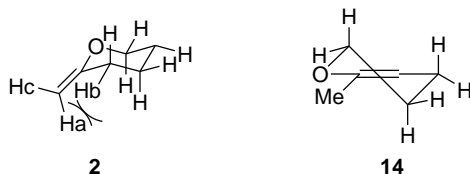


-ative effects and steric repulsions there exists an enthalpy difference of 8.7 kJ/mol between isomers **17** and **18**, with **18** existing as the lower energy isomer. Alternatively, the energy difference between corresponding enol ethers **2** and **14** was calculated to be 15.1-16.8 kJ/mol.⁴⁰ By subtracting the calculated hyperconjugative effects observed in the tetrahydropyranyl system (4.3 kJ/mol)⁴⁰ a large energy difference is still observed, greater than that of the carbocyclic system.

The difference in energy between the two systems cannot be based solely on non-bonding repulsions. In fact the heterocyclic system should have less steric repulsion between hydrogens

because a ring methylene group is replaced by an oxygen atom (Figure 1.4). With one less steric effect, the energy difference between the two heterocyclic isomers should be less than that between the carbocycles. However this is not observed, indicating that another factor contributes to dihydropyran **14**'s stability over exo enol ether **2**.

Figure 1.4



The third contributing factor towards endocyclic stability is the increased orbital overlap between the ring oxygen lone pairs and the olefin pi electrons.⁴⁰ If the ring oxygen is sp^3 hybridized, endo enol ether **14** can orient the oxygen lone pairs so that they fully overlap with the double bond's pi electrons (Figure 1.5). The steric arrangement of oxygen lone pairs and pi

Figure 1.5

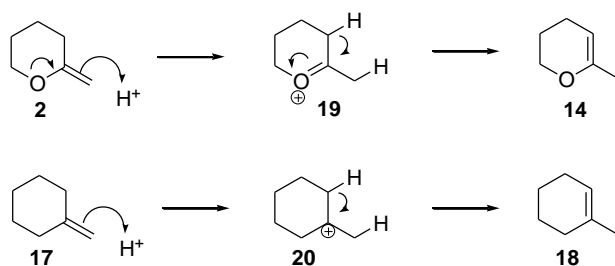


electrons yields an enol ether conformation that is analogous to the most stable methyl vinyl ether conformation. This orientation of orbitals causes endo enol ether **14** to have low energy because of the increased degree of resonance stabilization that can occur. Exo enol ether **2**, however, is forced to hold one of the lone pair of electrons equatorial and out of plane with the olefin's pi electrons (Figure 1.5). This steric arrangement does not result in an enol ether conformation with maximum orbital overlap, and hence lower resonance stabilization results.

Isomerization is thermodynamically favored in exo enol ether **2**. The isomerization is also kinetically driven by formation of the oxonium cation intermediate. The oxonium ion

intermediate **19** is more readily formed than the less stable carbocation intermediate **20** of the analogous all carbon system (Scheme 1.5).⁴⁰ Because exo enol ethers are prone to isomerization and hydrolysis, conditions employed toward their manufacture or subsequent chemistry must be carried out carefully without protic acids. However, exocyclic enol ether synthesis is routinely performed via elimination, cyclization or direct olefination.

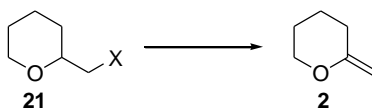
Scheme 1.5



Synthesis of Exocyclic Enol Ethers via Elimination

One of the most traditional routes for synthesizing exocyclic enol ethers involves the elimination of a leaving group, typically a halide, sulfonate,⁴⁴ or selenoxide,⁴⁵ (Scheme 1.6).

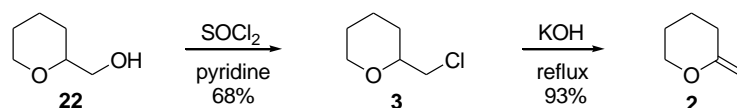
Scheme 1.6



Leaving group installation occurs at the exocyclic methylene position, adjacent to the anomeric center. A number of elimination conditions have proven successful in this transformation, however elimination can be accompanied with the formation of water and isomerization to the endocyclic enol ether **14**.⁴⁶ Use of elimination conditions in exocyclic enol ether formation is advantageous compared to other techniques in that often the reagents used are relatively inexpensive.

Commonly, thionyl chloride is used to prepare tetrahydropyranyl chloride **3** from 2-(hydroxymethyl) tetrahydropyran **22** (Scheme 1.7). Chloride **3** is transformed to desired exo enol ether **2** through elimination using KOH.⁴⁷

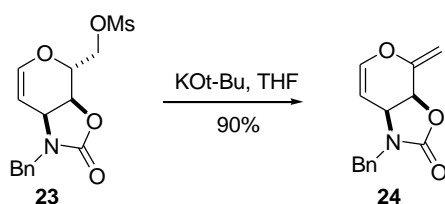
Scheme 1.7



Similar reactions, involving the elimination of a methylene halide at the anomeric position of a tetrahydropyran have been successfully performed through application of the following common bases: tBuOK ,⁴⁸ NaOH ,⁴⁹ KOH ,⁵⁰ NaH ,⁵¹ NaOMe ,⁵² DBU ,⁵³ and K_2CO_3 .⁵⁴ Silver fluoride has also facilitated elimination in a number of these systems.⁵⁵

Exo enol ethers have also been synthesized through base-induced elimination of mesylates (Scheme 1.8).⁴⁴ Mesylate **23** was formed via the corresponding primary alcohol. Addition of the sulfonate group aids in activating this group towards elimination. Subjection of mesylate **23** to potassium tert-butoxide gives rise to the exocyclic enol ether **24** in good yield.

Scheme 1.8

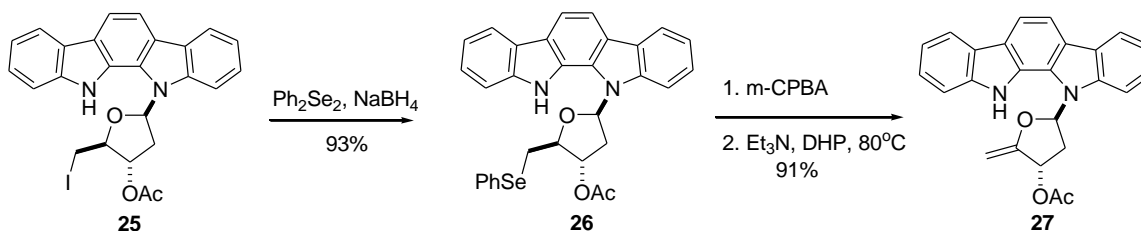


Phenyl selenides can be transformed into exocyclic enol ethers through oxidation and subsequent elimination of the selenoxide. This reaction is not as common as the related elimination of halogens because it involves formation of selenium byproducts and involves more synthetic steps. Enol ether **27** has been synthesized for use in the total synthesis of bioactive alkaloid (+)-K252a.⁴⁵

Intermediate enol ether **27** was synthesized from iodide **25** in three steps (Scheme 1.9).

Initial attempts and dehydroiodination failed to yield the desired enol ether, instead

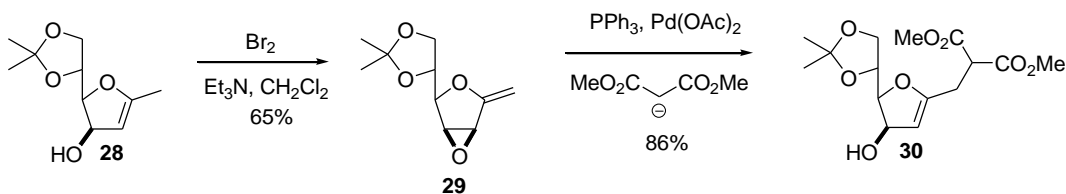
Scheme 1.9



resulting in an unwanted byproduct. Therefore a second route was employed for conversion of iodide **25** to the exo enol ether **27**. Iodide **25** was converted to phenyl selenide **26** with diphenyl selenide and sodium borohydride.⁵⁶ Selenide **26** was subsequently oxidized to the selenoxide, which was directly subjected to heat-induced elimination conditions.⁵⁷ Exo enol ether **27** resulted without byproduct formation.

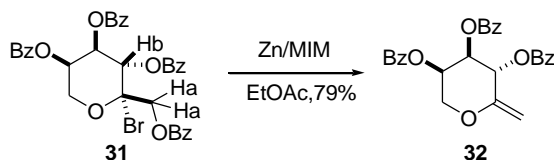
Epoxy-2-methylenetetrahydrofurans **29** have been effectively synthesized from corresponding glycals **28** in a one-pot synthesis (Scheme 1.10).⁵⁸ First dihydrofuran **28** was subjected to bromination. Basic conditions effect concurrent epoxide formation, and elimination to produce epoxide target **29**. This exo enol ether could subsequently be used as an electrophile, and produced alcohol **30** after palladium catalyzed (20 mol %) addition of dimethyl malonate.

Scheme 1.10



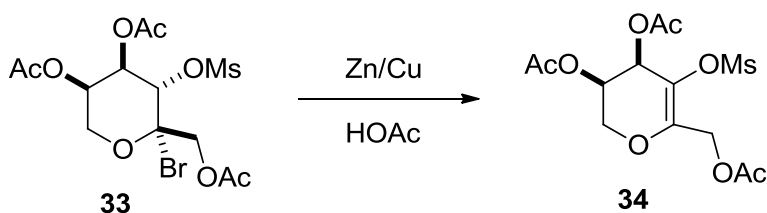
Exocyclic enol ethers have been selectively formed from anomeric bromides. Bromoketose **31** was converted to the corresponding exocyclic enol ether by modified Fisher-Zanch conditions (Scheme 1.11).⁵⁹ Bromide **31** was reductively eliminated with zinc dust and

Scheme 1.11



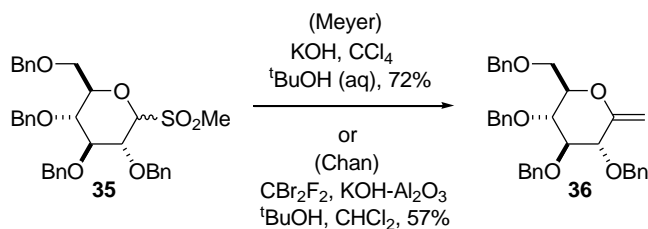
N-methyl-imidazole (MIM) to provide enol ether **33** in 79% yield along with 11% of the endocyclic isomer. Exocyclic enol ether **32** predominates because the terminal hydrogens (Ha) are more accessible towards elimination than the secondary cyclic proton (Hb). The kinetic conditions of this reaction favor the exo enol ether formation and little isomerization occurs. Alternatively, the use of Zn/Cu and acetic acid on a similar substrate favored endo product **34** under thermodynamic conditions (Scheme 1.12).

Scheme 1.12



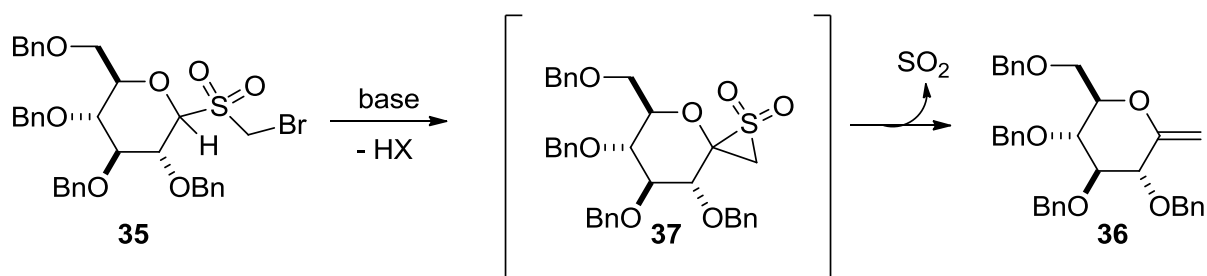
The Ramberg-Bäcklund rearrangement has been used effectively to form exocyclic enol ethers from sulfones (Scheme 1.13).⁶⁰ Methylsulfone **35** can be subjected to either standard

Scheme 1.13



Meyer conditions⁶¹ or milder Chan conditions⁶² to provide enol ether **36**. In both cases halogen transfer is followed by deprotonation. The carbanion that results arranges into an unstable thiirane dioxide that decomposes through elimination of sulfur dioxide (Scheme 1.14). The same conditions have been applied to enantiopure sulfones bearing longer carbon chains to yield substituted enol ethers with some E:Z selectivity.^{60a}

Scheme 1.14



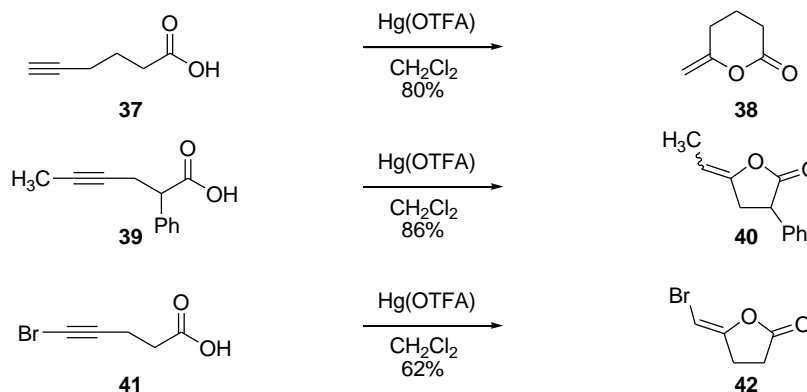
Synthesis of Exocyclic Enol Ethers via Intramolecular Cyclization

Exocyclic enol ethers have been synthesized via intramolecular cyclization of alkynyl alcohols, alkynyl carboxylic acids, vinyl halides, and hydroxy alkenes via metal and lanthanide catalysts. This technique involves both cyclization and the formation of an exo double bond in one step. A number of elements have been utilized for these cyclization reactions including catalysts containing mercury, silver, palladium, copper, gold, rhodium, and various lanthanides. The cyclizations prove to be useful methods for exo enol ether synthesis, especially from linear precursors.

Alkynyl carboxylic acids and alcohols were first cyclized through the use of mercury catalysts.⁶³ Katzenellenbogen created simple and substituted exocyclic enol ether lactones **38** and **40** and halo enol ether lactones **41** via corresponding acetylenic acids **37**, **39**, and **41** using catalytic Hg(OTFA)₂ (Scheme 1.15).⁶⁴ Use of mercury acetate in the same reaction was less effective, resulting in lower yields and longer reaction times. The lower yield observed for the

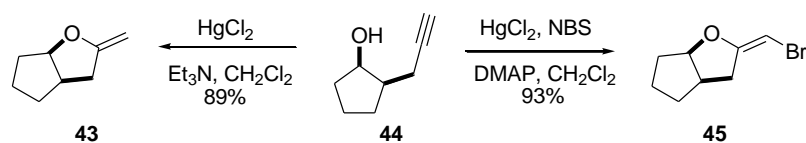
reaction involving carboxylic acid **41** is most likely due to a lack of positive charge stabilization at the β carbon. Halogenated acetylenic acids experience inductive destabilization of the intermediate cation created after mercury addition. Additionally, dehalogenation accompanies the reaction which substantially lowered yield.

Scheme 1.15



Schwartz demonstrated the manufacture of exocyclic enol ethers through mercury activation (Scheme 1.16).⁶⁵ A variety of mercury species effected cyclization including HgCl_2 , $\text{Hg}(\text{OAc})_2$, and $\text{Hg}(\text{OCOCF}_3)_2$ although mercury acetate provided the best yields. Enol ether **43**

Scheme 1.16

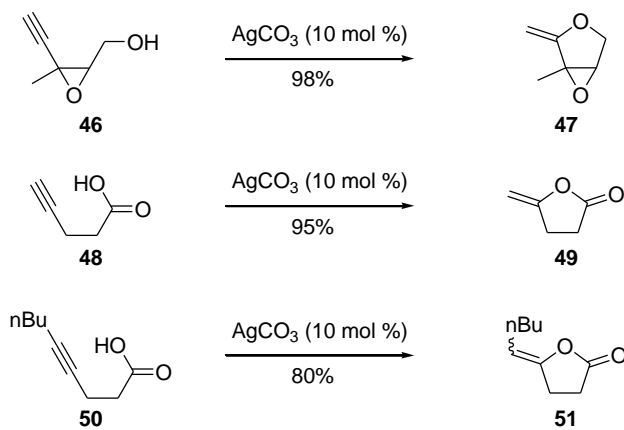


was created from the cyclization of alkynyl alcohol **44**. Interception of the organomercury intermediate by NBS yielded bromo enol ether **45** from alcohol **44**. Similarly, Villemin utilized HgO and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to transform internal alkynes into substituted enol ethers.⁶⁶

The cyclization of alkynyl alcohols and acids under silver catalysis has received little study. Silver carbonate (10 mol %) has induced cyclization of both acetylenic alcohol **46** and acids **48** and **50** to the corresponding exocyclic enol ethers **47**, **49**, and **51** (Scheme 1.17).⁶⁷ The

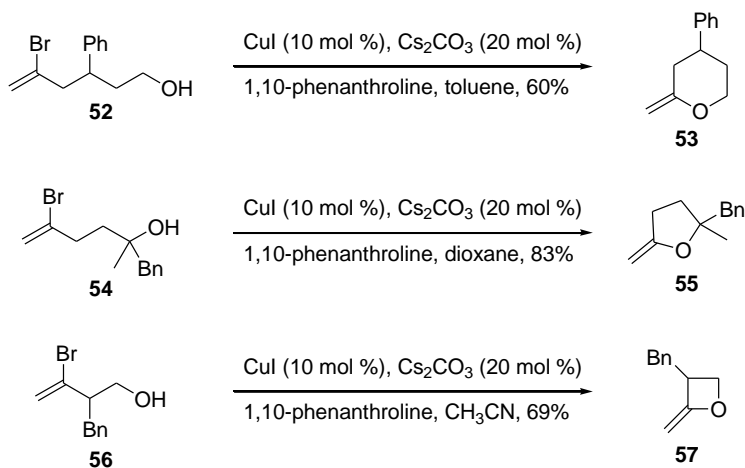
reactions involving terminal alkynes **46** and **47** reached near quantitative yields of the desired products. Cyclization of acid **50** was less effective and resulted in a 1:1 mixture of E:Z isomers. Silver oxide and silver acetate also facilitated the conversion of acetylenic alcohol **46** to enol ether **47**, albeit in lower yields and over a longer period of time (80%, 40 min and 80%, 30 min respectively as compared to 98%, 15 min for silver carbonate).

Scheme 1.17



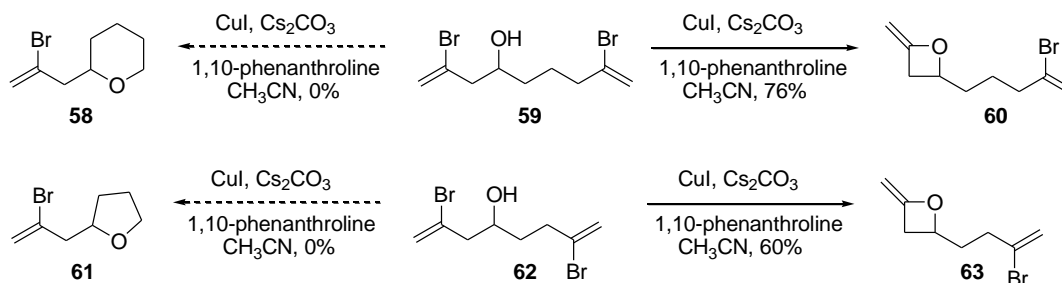
Cyclizations involving copper catalysis have also been studied. Vinyl bromides were coupled, intramolecularly, to alcohols using copper iodide to form 6, 5, and 4-membered exocyclic enol ethers (Scheme 1.18).⁶⁸ Hexene **52** was cyclized to 2-methylenetetrahydropyran

Scheme 1.18



53 in modest yields. 2-Methylenetetrahydrofuran **55** was formed from alkenyl bromide **54**, and even strained four-membered ring **57** was successfully manufactured from butene **56**. In fact the four-membered exo enol ethers were created preferentially (Scheme 1.19).

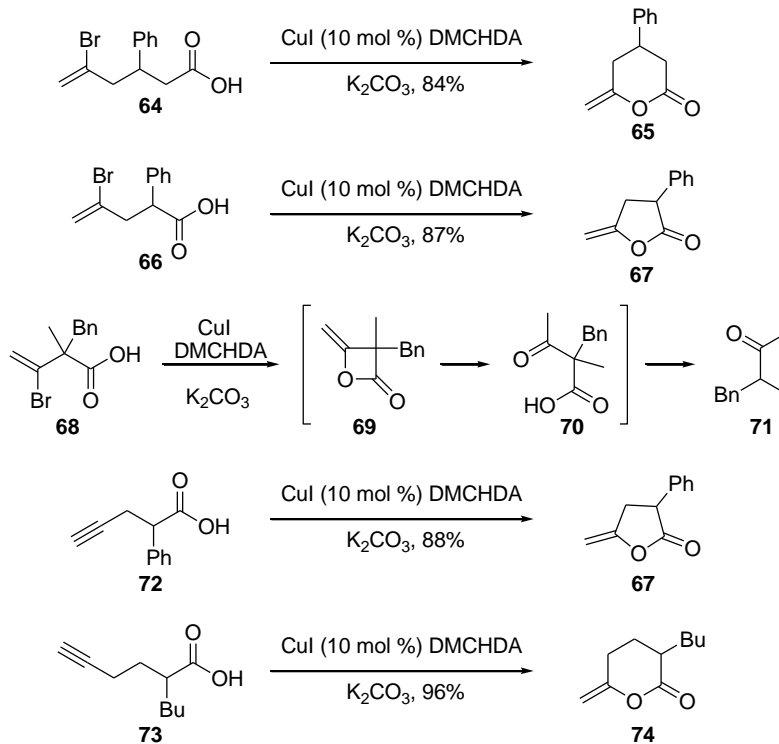
Scheme 1.19



Cyclization to form four-membered exocyclic enol ethers was preferred over formation of the six and five-membered rings. All of the ring closure reactions are permissible by Baldwin's rules,⁶⁹ however, the 4-*exo-trig* cyclization is sterically favored. This preferred cyclization involves a 5-membered transition state that is thermodynamically favored and more sterically attainable than either the 5-*exo-trig* or 6-*exo-trig* cyclizations. If a palladium catalyst (Pd(OAc)₂/BINAP) is used as a catalyst in place of copper iodide, formation of the 5-*exo* products was preferred over the 4-*exo* products. Thus, tetrahydropyran **58** and tetrahydrofuran **61** were alternatively formed from dibromodienes **59** and **62** respectively. A Pd(0) 5-membered transition state is not sterically preferred in these reactions because Pd(0) is much larger than Cu(I), which effects the transition state geometry.

Copper iodide has also induced formation of enol lactones from carboxylic acids.⁷⁰ Two methods were used to form the enol lactones: cyclization of bromoenoic acids and cycloisomerizations of alkynoic acids. The first method utilizes copper iodide as a cross-coupling catalyst in a modified Ullmann coupling. Best yields were obtained using a N,N'-dimethylcyclohexane-1,2-diamine (DMCHDA) ligand. Both 6-*exo* (**65**) and 5-*exo* (**67**) products

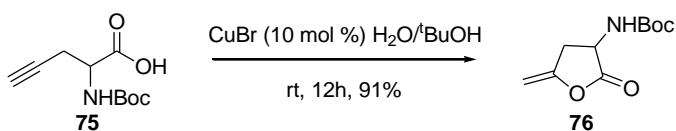
Scheme 1.20



were synthesized in good yields (Scheme 1.20). 4-Exo products like **69** were not isolated, but instead provided ketone **71**. Presumably the strained enol lactone undergoes ring-opening and subsequent decarboxylation, leading instead to the isolation of ketone **71**.

Application of the modified Ullman conditions to alkynoic acids provided enol lactones in good yields without any further optimization. Pent-4-ynoic (**72**) and hex-5-ynoic (**73**) acids were successfully cyclized to enol lactones **67** and **74**. Similarly, Mindt and Schibli discovered that amine-containing alkynoic acids like **75** were capable of cycloisomerization to enol lactones **76** using CuBr in aqueous media (Scheme 1.21).⁷¹

Scheme 1.21



Gold catalysts have recently received attention for their ability to induce alkyne cyclization reactions. AuCl was used to cyclize acetylenic acids to form exocyclic enol lactones (Table 1.1).⁷² 5, 6, and 7-membered enol lactones were synthesized. Electrophilic activation of the alkyne by AuCl facilitates intramolecular cycloaddition of the deprotonated lactone. Acids **48** and **37** were successfully converted to enol lactones

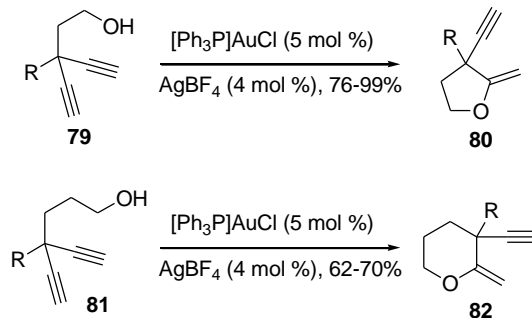
Table 1.1: Gold Catalyzed Cyclization of Acetylenic Acids

Entry	Acetylenic acid	Lactone	Yield
1			96
2			97
3			25

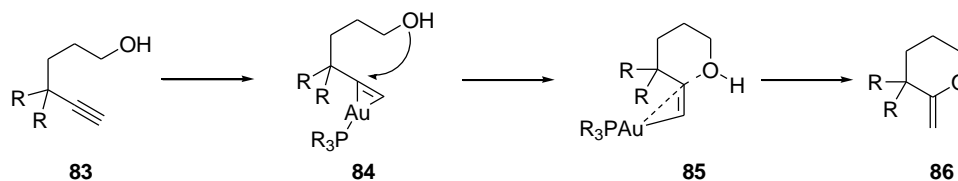
49 and **38** in near quantitative yields. The reaction of acetylenic acid **77** with AuCl, alternatively afforded enol lactone **78** in low yield over a longer period of time (48 h). Nonetheless the exo products were always preferentially formed instead of endo cyclization products.

Cyclization of diacetylenic alcohols with AuCl and AgBF₄ have provided 5-(**80**) and 6-membered (**82**) exocyclic enol ethers in good yields (Scheme 1.22).⁷³ Because the enol ethers are sensitive to acidic conditions, the catalyst loading of AgBF₄ was kept below that of the gold catalyst. The gold catalyst coordinates to the alkyne, forming metallacyclopropene **84**. Intramolecular attack of the propene by the alcohol yields a vinyl gold intermediate that is protodeaurated to form enol ether **86** (Scheme 1.23).

Scheme 1.22

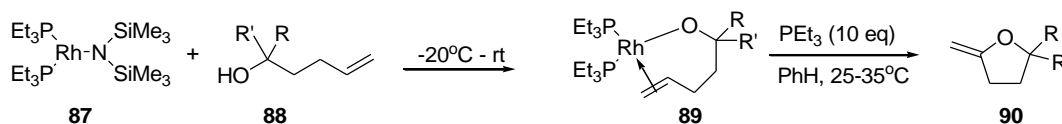


Scheme 1.23



Rhodium metal has facilitated cyclization of hydroxy alkene **88** to exo enol ether **90** (Scheme 1.24).⁷⁴ This example differs from others because an olefin is acting as the cyclic precursor. Coordination of alkene **88** with rhodium complex **87** yielded rhodium alkoxide **89**.

Scheme 1.24

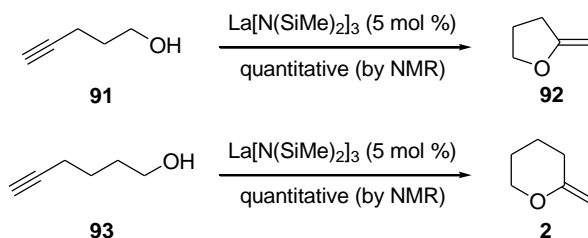


The coordination results in the loss of the silylamide ligand. After isolation of intermediate **89**, excess triethylphosphine is added and facilitates oxidative insertion of the hydroxyl group into the double bond. Insertion is followed by reductive elimination of the rhodium catalyst to yield the 2-methylenetetrahydrofuran **90**.

Lanthanide catalysis has been used to transform alkynyl alcohols into enol ethers. Exocyclic enol ethers **92** and **2** were formed from the cyclization of alcohols **91** and **93** in the presence of lanthanide amide complexes $\{\text{Ln}[\text{N}(\text{SiMe}_3)_2]_3$, Ln = La, Nd, Sm, Y, and Lu (Scheme

1.25).⁷⁵ Quantitative yields of enol ethers **92** and **2** were obtained by ¹H NMR analysis. The mechanism of the reaction involves slow alkyne insertion followed by rapid substrate protonolysis.

Scheme 1.25

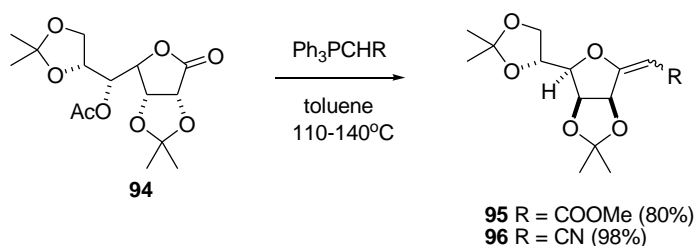


Synthesis of Exocyclic Enol Ethers via Direct Methylenation

The most direct method for exo enol ether synthesis involves the direct methylenation of the corresponding lactones with phosphorus-based or organometallic reagents. Typically Wittig-type reactions are not effective at this transformation, although trisubstituted exocyclic enol ethers and dihaloolefins⁷⁶ can be prepared in this way. Lactones **94** react with stabilized phosphoranes to form trisubstituted, conjugated products **95** and **96** (Scheme 1.26).⁷⁷ Elevated temperatures or microwave irradiation was required to facilitate these reactions and little to no Z/E selectivity was observed.

Generally, methylene enol ethers **2** are better prepared using organometallic reagents. The Tebbe⁷⁸ and Petasis⁷⁹ reagents are most commonly used in these organometallic olefination

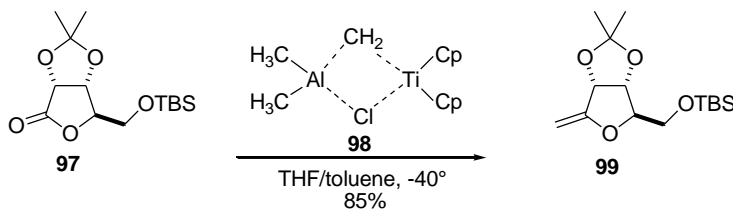
Scheme 1.26



processes. Limited examples also make use of zinc/titanium(I) chloride mixtures,⁸⁰ triethylphosphine-based titanium reagents,⁸¹ and titanium(IV) chloride/magnesium combinations.⁸² The advantage of using these titanium-based reagents is that aqueous work-ups are not required, which is important in avoiding hydrolysis and possible isomerization in these labile enol ethers.

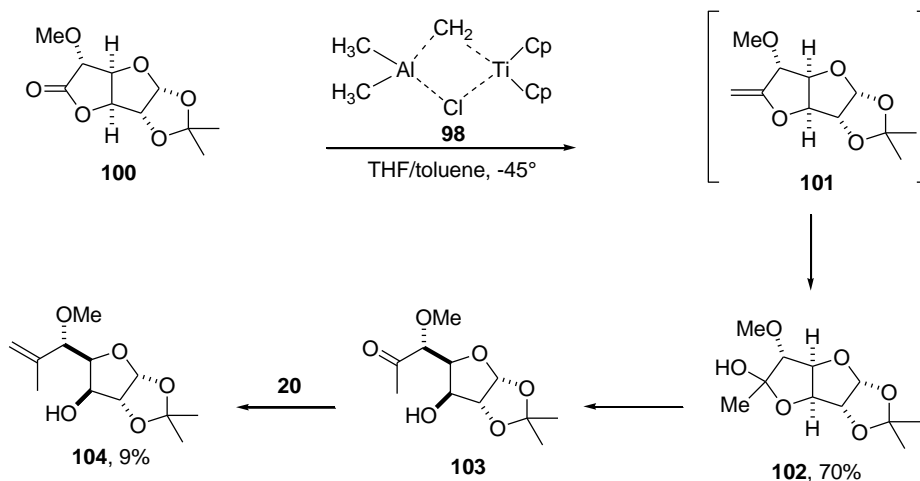
The first use of organotitanium complexes was reported using the Tebbe reagent (**98**).⁸³ Initially the Tebbe reagent was applied to esters as a new method for synthesizing enol ethers from esters.⁷⁸ A protocol had not previously been devised for the direct olefination of esters. Thereafter the Tebbe reagent was applied toward 5 and 6-membered exocyclic enol ether synthesis (Scheme 1.27).⁸⁴ Wilcox manufactured exocyclic enol ethers for use in C-glycoside synthesis. Wilcox used Tebbe's reagent (**98**) to convert lactone **97** into exocyclic enol ether **99** in high yield, thus validating use of the Tebbe reagent towards the synthesis of these moieties.

Scheme 1.27



Use of Tebbe reagent towards the synthesis of enol ether **101** however, resulted in unwanted, hydrolyzed products. Application of Tebbe reagent to bicyclic γ -lactone **100** yielded unexpected products **102** and **103** (Scheme 1.28).⁸⁵ Here, initial formation of the enol ether **101** was quickly followed by hydrolysis to give alcohol **102**. Ring-opening of bicycle **102** leads to ketone **103**, which subsequently undergoes a second methylenation to provide biproduct **104**.

Scheme 1.28



The Tebbe reagent has generally been effective toward the synthesis of exo enol ether, however there are several drawbacks of this method. The Tebbe reagent is relatively unstable and must be synthesized just prior to use from trimethyl aluminum and titanocene dichloride. The reagent also contains aluminum resulting in manufacture of aluminum salts after product synthesis. These aluminum salts can be difficult to remove from the product mixture, resulting in lower yields.

An alternative protocol for lactone olefination was developed by Petasis. This method employed the use of dimethyltitanocene (**106**), which can be easily prepared from titanocenedichloride (**105**) and methyllithium in either diethylether or toluene (Scheme 1.29).⁸⁶ Benefits of using the Petasis reagent over Tebbe's reagent include a shorter, less expensive preparation, longer shelf life (when stored as a solution in THF or toluene), enhanced stability, and a lack of residual aluminum reagents.

Scheme 1.29



Like Tebbe, the Petasis olefination has been used successfully for the conversion of aldehydes, ketones, esters, and lactones to their corresponding olefins. Because lactones and esters are less reactive than ketones or aldehydes, the olefination of these functional groups occurred over a longer period of time. Petasis discovered that methylenation of lactones and esters was optimized by using two equivalents of dimethyltitanocene.

A number of different types of lactones are capable of undergoing Petasis olefination. Examples of 5, 13, and 6-membered lactones that have been converted to exo enol ethers using the Petasis olefination method are shown in Table 1.2.⁸⁶ Lactone **107** was converted to exo enol

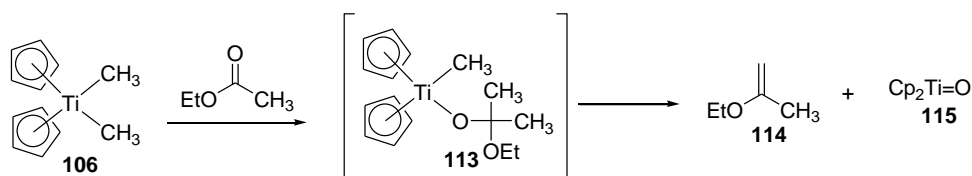
Table 1.2: Petasis Olefination of Lactones

Entry	Lactone	Product	Yield
1	 107	 108	41%
2	 109	 110	70%
3	 111	 112	80%

ether **108** in moderate yield while the 13-membered lactone **109** provided enol ether **110** in fairly good yield. Petasis olefination was also effective in converting aromatic-containing lactone, dihydrocoumarin **111**, to exocyclic enol ether **112**.

The mechanism of the Petasis reaction was first proposed by Petasis.⁸⁷ Petasis proposed that olefination occurred through a mechanism involving acyclic intermediates (Scheme 1.30). It was theorized that dimethyl titanocene **106** complexes with the ester carbonyl. Complexation is

Scheme 1.30

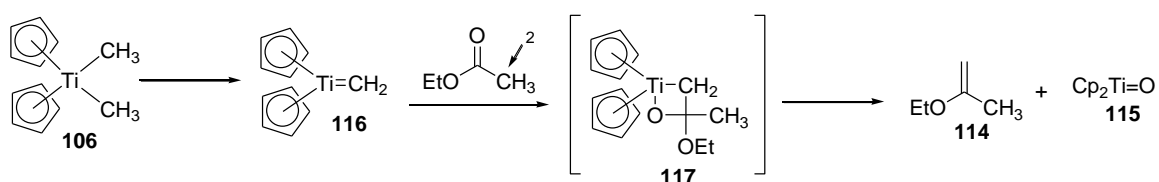


followed by migratory insertion of the ester into the titanium complex, which provides acyclic intermediate **113**. This insertion involves methyl transfer from dimethyl titanocene **106** to the ester. Reductive elimination of titanium complex **113** results in the loss of methane and production of enol ether **114** and titanoceneoxide **115**. By this mechanism, complexation is viewed to be the rate-determining step. Therefore the reaction kinetics should be second order and based on both the concentration of ethyl acetate and titanocene dichloride.

Petasis based his mechanistic hypothesis on his deuterium labeling studies. Hydrogen/deuterium scrambling occurred both in reactions of protio dodecyl acetate with $\text{Cp}_2\text{Ti}(\text{CD}_3)_2$ and dodecyl acetate- d_3 with $\text{Cp}_2\text{Ti}(\text{CH}_3)_2$. In both cases, Petasis's proposed mechanism accounts for deuterium incorporation into the product or methane biproduct respectively. In either deuterium experiment, once methyl transfer is complete and intermediary complex **113** is formed, there is a 50% chance that the deuterated methyl group is transferred to the enol ether product or methane biproduct.

Hughes⁸⁸ and Eberlin⁸⁹ have each performed additional experiments that refute Petasis's proposed olefination mechanism. Hughes proposed that enol ether **114** was formed through titanium carbene intermediate **116** (Scheme 1.31). Reductive elimination of methane from dimethyl titanocene **106** results in formation of titanium carbene species **116**. Addition of an ester to carbene **116** yields oxatitanacycle **117**. Subsequent retrocyclization of cyclic intermediate **117** provides enol ether **114** and titanoceneoxide **115**. Research performed by Eberlin supported the Hughes mechanism by detecting protonated versions of oxatitanacyclo **117** using tandem mass spectrometry.⁹⁰

Scheme 1.31



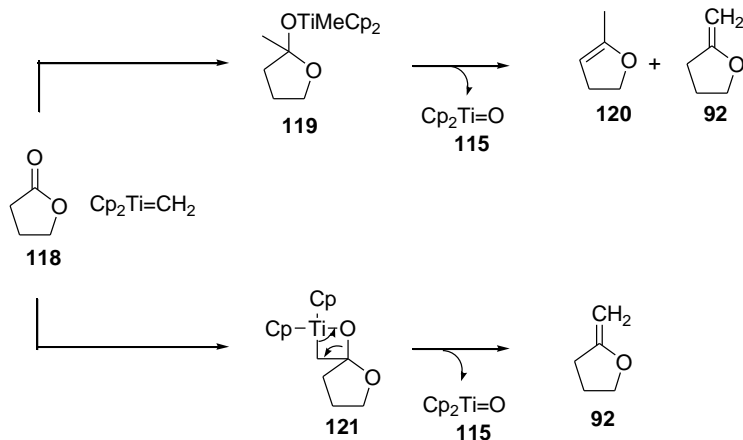
Both isotopic labeling studies and kinetic experiments provided evidence for the revised Petasis mechanism. The reaction of ethyl acetate, ^{13}C labeled at the C_2 position, with dimethyl titanocene yielded products that did not incorporate ^{13}C at the methylene carbon.⁸⁹ This evidence supports the Hughes' methylenation mechanism. Via the Petasis mechanism there should be a fifty percent incorporation of the labeled carbon in the newly formed olefin. Both methyl groups of intermediate **113** are equivalent and are equally likely to form the methylene carbon of enol ether **114**. The Hughes' proposed mechanism, alternatively, should not incorporate ^{13}C into the methylene position of enol ether **114** because the labeled carbon is never part of oxatitanacycle intermediate **117**. The ^{13}C labeling study is a more reliable method for mechanistic study than the deuterium labeling used by Petasis because carbon labeling avoids potential deuterium/hydrogen exchanges with cyclopentyl diene hydrogens.⁹⁰

Furthermore, kinetic studies proved that the reaction is zero order in ethyl acetate, indicating that ethyl acetate is not involved in the rate-determining step.⁸⁹ This observation is consistent with a mechanism involving a carbene intermediate (Scheme 1.31), but again does not agree with the Petasis mechanism, which involves both dimethyltitanocene and ethyl acetate in the rate-determining step. For the methyl addition mechanism (Scheme 1.30) the reaction is expected to be first order both in dimethyltitanocene and the ester. Secondly, if the rate-determining step of Petasis olefination is independent of the ester, as proposed by Hughes, reactions of electronically and sterically diverse esters should result in similar reaction rates. The similarity of olefination reaction rates observed by combining both ethyl acetate and phenyl methyl ester with dimethyltitanocene verified that esters aren't involved in the rate-determining step.

Hughes' third set of experiments showed a large primary kinetic isotope effects when $\text{Cp}_2\text{Ti}(\text{CD}_3)_2$ was used in a reaction with both dodecyl acetate and ethyl acetate. The primary kinetic isotope effect that is observed indicates loss of a methyl group in the rate-determining step of the reaction. The carbene olefination mechanism, opposed to the Petasis mechanism, involves the loss of methane from dimethyltitanocene in the rate-determining step. Only a small secondary isotope effect would be expected by the Petasis mechanism. Additionally, observations from this deuterium study did not demonstrate hydrogen/deuterium scrambling, which is consistent with the ^{13}C isotope studies.

Finally, the regiochemical outcome of the exo enol ether products is inconsistent with the Petasis mechanism. In this proposed mechanism titanocene intermediate **119** is formed and subsequently eliminated (Scheme 1.32). In theory elimination should occur to form the more

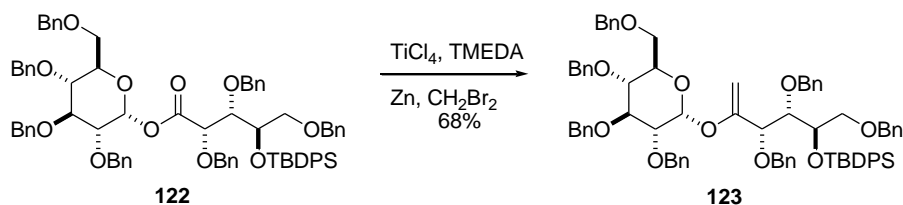
Scheme 1.32



stable trisubstituted endocyclic enol ether **120** as a major product. In practice, little endocyclic enol ether is formed in these reactions, and seems to arise from isomerization of the exocyclic product. A regiospecific carbene-mediated mechanism is more consistent with this observation.

A third titanium catalyzed protocol for one-step olefination was reported using 1,1-dibromoalkanes, zinc, titanium(IV)chloride, and TMEDA (Takai-Lombardo reagent) (Scheme 1.33).⁸⁰ In this process the catalyst is generated *in situ* from commercially available starting

Scheme 1.33



materials, which is a major advantage. This method is useful for the conversion of esters to enol ethers, but less so for the olefination of lactones. Interestingly ester **122** was converted to enol ether **123** by Takai-Lombardo olefination, but application of the Tebbe reagent to the same system was unsuccessful.⁹¹ A number of different esters could be converted to enol ethers through Takai alkylidenation (Table 1.3).⁸⁰ The reaction provided a mixture of Z-selective

Table 1.3: Manufacture of *E* versus *Z* Isomers with Takai-Lombardo Olefination

$$\text{R}-\text{C}(=\text{O})-\text{OR}' + \text{R}''\text{CHBr}_2 \xrightarrow[\text{Zn}]{\text{TiCl}_4, \text{TMEDA}} \text{R}-\text{C}(\text{OR}')=\text{CH}-\text{R}''$$

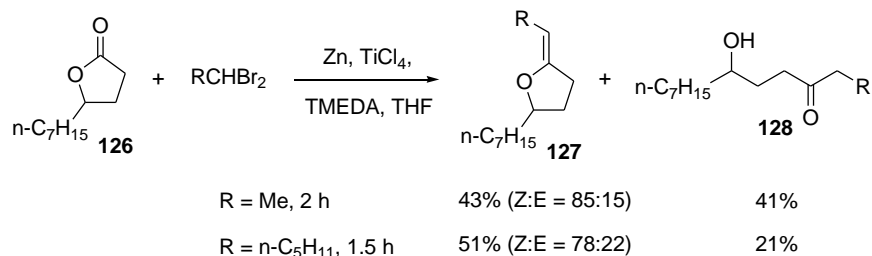
124 **125**

Entry	R	R'	R''	Yield (%)	Z/E
1	Ph	Me	Me	86	92/8
2	Ph	Me	i-Bu	79	96/4
3	Ph	t-Bu	Me	81	71/29

stereoisomers. The *Z*-isomer formed preferentially to minimize the steric repulsion between R and R' groups in olefin **125**. As the size of the R or R'' groups increase, the selectivity increases, which is observed when the R'' group is changed from a methyl to a iso-butyl group (Table 1.3, entries 1 and 2). The opposite effect occurs when the size of the R' group is increased. When R' is changed from methyl to tert-butyl the Z/E selectivity decreased because a competing steric repulsion exists between the R'' and R' groups, increasing the formation of the *E* isomer (Table 1.3, entries 1 and 3).

Use of this methodology toward exo enol ether synthesis is complicated by hydrolysis. Significant amounts of hydrolysis products **128** were formed in addition to the desired, substituted exocyclic enol ethers **127** (Scheme 1.34).⁸⁰ The Z/E stereoselectivity of this process

Scheme 1.34

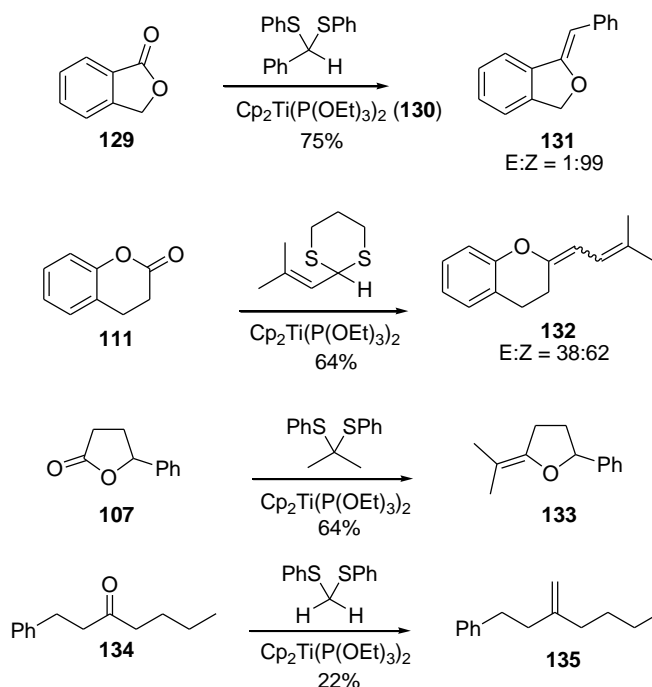


is similar to that seen for the Takai alkylation of esters (Table 5.1). Currently there are no reports of simple methylenetetrahydropyran preparation using the Takai-Lombardo protocol.

In a related process, Takeda reported the synthesis of substituted enol ethers from thioacetals (Scheme 1.35).⁸¹ In this olefination process, titanium species **130** was synthesized from triethyl phosphite and titanocene dichloride. Complex **130** was combined with dithioacetals and carbonyl-containing compounds to yield the corresponding olefins.

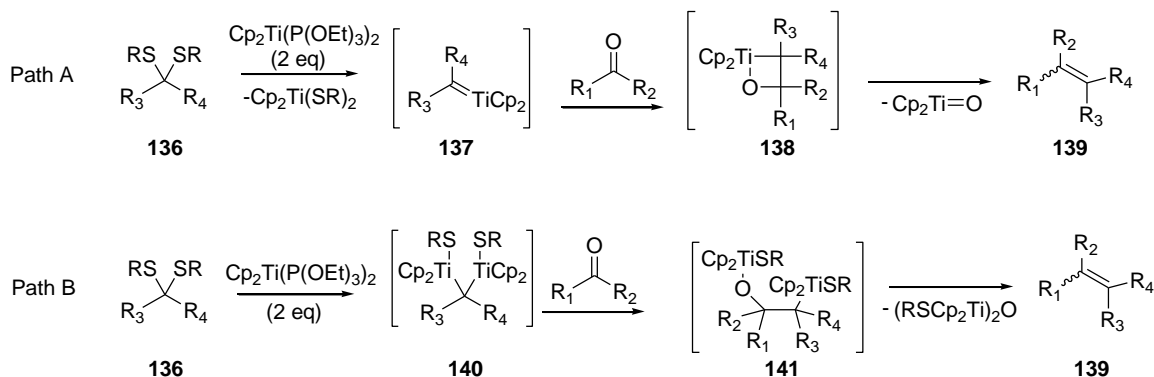
This methodology proved useful with transforming aldehydes, ketones, esters, and lactones into olefins and is effective for synthesizing conjugated dienes with modest selectivity based on steric repulsion, similar to the Takai examples.⁸⁰ Only the synthesis of tri- (**131** and **132**) and tetra-substituted (**133**) exocyclic enol ethers were demonstrated. This process was also used to prepare geminally disubstituted alkenes **135** from ketone **134**. The formation of simple enol ethers like **2** was not reported in the communication.

Scheme 1.35



This reaction could proceed through one of two pathways. The first proposed mechanism (Path A, Scheme 1.36) involves the addition of dithiane **136** to the phosphate-titanium complex, which is accompanied with sulfur-titanium complex removal, resulting in formation of intermed-

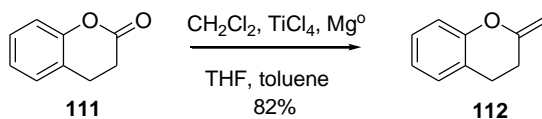
Scheme 1.36



iate **137**. Addition of complex **137** with a carbonyl creates oxatitanocyclobutane intermediate **138**. Intermediate **138** undergoes anti 2+2 addition to yield olefin **139** and titanocene oxide. An alternate proposed pathway (Path B, Scheme 1.36) proceeds through insertion of two equivalents of the titanium complex into the carbon sulfur bonds of dithiane **136**. Addition of this gem-dimetallated species to a carbonyl yields intermediate **140**, which undergoes elimination to olefin **139**.

More recently, a CH_2Cl_2 -Mg-TiCl₄-THF system has been devised for the conversion of esters into their corresponding olefinated products.⁸² This process involves a dichloromethane-derived methylene transfer to an ester through use of a bimetallic complex (Mg-TiCl₄). Although this process has not been thoroughly studied for its use on lactones, dihydrocoumarin **111** was successfully converted to the corresponding exocyclic enol ether **112** by this method (Scheme 1.37). Initially, only a 40% yield of enol ether **112** was isolated due to unwanted isomerization. Altering the solvent system from THF to 50% THF and 50% toluene, however, produced desired product **112** in good yield.

Scheme 1.37



The synthesis of exo enol ethers is key towards our methodology studies. The synthetic methods used by our group focus mainly on elimination and titanium-mediated olefination processes. Elimination is used as one of the methods, because access to the corresponding precursors is fairly straightforward and works with our synthetic strategy. Petasis olefination is also applied to a number of lactones, providing exo-enol ethers for the methodology studies. Petasis olefination is utilized for several reasons: The process can be applied to a wide variety of lactones without altering reaction kinetics, the methylenating reagent is relatively stable when properly stored, and the lactone precursors are generally stable intermediates.

1.4 Reactions of 2-Methylenetetrahydropyrans

Although exocyclic enol ethers are portrayed as labile functional groups that are prone to isomerization and hydrolysis, a wide variety of reactions have been applied to these moieties. Often these enol ethers act as alkenes in addition reactions, but have been reported in a number of other bond-forming reactions as well. Exo enol ethers have been repeatedly used as substrates in rearrangements, pericyclic reactions, radical reactions, and have been used as both electrophiles and nucleophiles. The carbon-carbon bond forming techniques of these enol ethers is of special interest to organic chemists, because of the application toward natural product synthesis. The use of 2-methylenetetrahydropyrans as nucleophiles, especially in carbon-carbon bond forming processes, has received limited attention. The research focus in our group is to demonstrate the inherent ability of 2-methylenetetrahydropyrans as nucleophiles in carbon-carbon bond forming reactions.

Addition Reactions

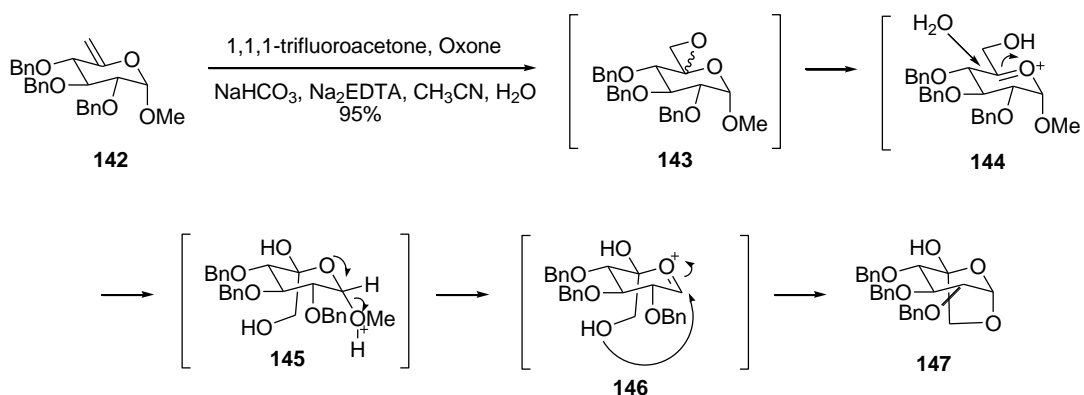
Many of the addition reactions of alkenes can be applied to exocyclic enol ethers. Addition reactions on chiral substrates like exo-glycols can yield stereoselective products due to

chiral induction from the substrate. Addition reactions of enol ethers include hydrogenation, oxidative additions, carbene addition processes, and hydroboration. The addition of carbenes and boron to the enol ether are the most meaningful transformations because these processes facilitate the manufacture of new carbon-carbon bonds.

The addition of hydrogen to exo enol ethers results in formation of the corresponding tetrahydropyrans. Hydrogenation proceeds stereoselectively from the less hindered face of the 2-methylenetetrahydropyran.⁹² Typical reduction conditions are suitable for exo enol ether hydrogenation and include the use of palladium,⁹³ rhodium,⁹⁴ platinum,⁹⁵ nickel,⁹⁶ and enantioselective ruthenium binol-derived catalysts.⁹⁷

Oxidative additions to exo enol ethers include epoxidation and dihydroxylation processes. Exo enol ether derived epoxides are synthesized using standard conditions (mCPBA⁹⁸ or dimethyldioxirane⁹⁹) and can be subsequently subjected to nucleophilic attack, affording the corresponding alcohols. An intramolecular example of this process involves epoxidation of enol ether **142** (Scheme 1.38).¹⁰⁰ Epoxidation occurs via *in situ* formation of

Scheme 1.38

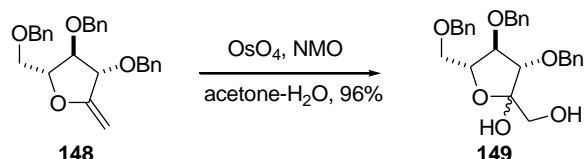


methyl(trifluoromethyl) dioxirane from oxone and 1,1,1-trifluoroacetone to afford epoxide **147**.¹⁰¹ Subsequent hydrolysis of oxonium ion **144**, resulting from the opening of epoxide **143** yields diol **145**. Concomitant oxonium ion formation and methanol elimination provides

intermediate **146**. Intramolecular attack of the oxonium ion by the primary alcohol provided bicycle **147**.

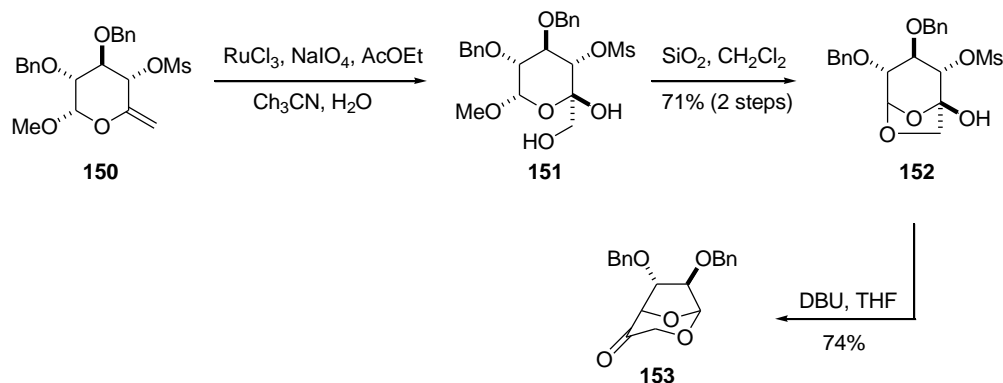
Metal-mediated dihydroxylations of exo enol ethers have been reported using osmium and ruthenium metals. Osmylation of *exo*-glycal **148** yielded epimeric diol **149**, which was isolated as the hemiketal rather than the ring-opened ketone isomer (Scheme 1.39).¹⁰² Use of ruthenium(III) chloride and sodium periodate also provided dihydroxylated products. Under

Scheme 1.39



these oxidative conditions, enol ether **150** was converted to diol **151**. (Scheme 1.40).¹⁰³ Addition occurred to the top face of 2-methylenetetrahydropyran **150**, opposite to the axial C₆

Scheme 1.40

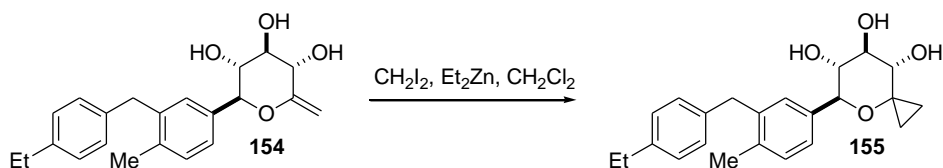


methoxy substituent. Cyclization by silica gel chromatography, and DBU-induced rearrangement afforded bicycle **153**, which could be used as a synthetic precursor to zaragozic acid natural products.

Carbene additions to exocyclic enol ethers are effective methods of carbon-carbon bond formation. Simmons-Smith conditions,¹⁰⁴ addition of dihalocarbenes derived from chloroform or

bromoform,¹⁰⁵ and metal-mediated carbene additions¹⁰⁶ all afforded the corresponding cyclopropanes which were studied for their biological activity or could be carried on to more complex natural products. Robinson et al. sought the discovery of new SGLT2 inhibitors that prevent re-uptake of filtered glucose from pro-urine and therefore aid in the treatment and prevention of diabetes.¹⁰⁵ The researchers made modifications to the glycoside portion of dapagliflozin, a diabetes drug candidate in phase 3 clinical trials, hoping to discover additional drug targets. As part of this effort, spirocyclopropyl tetrahydropyran **155** was synthesized from enol ether **154** under standard Simmons-Smith conditions (Scheme 1.41). Although no yield

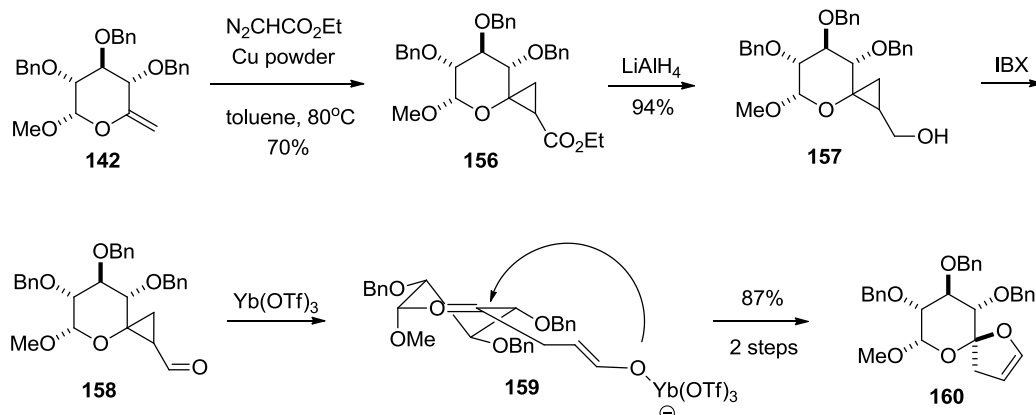
Scheme 1.41



was reported for this step, the biological activity of spirocyclopropane **155** was evaluated. Spirocyclopropane **155** displayed potent activity against SGLT2 with an IC₅₀ value of 3.0 nM. In spite of the high bioactivity, the short half-life of this molecule, when applied to live rat models, prevented further advancement of this molecule as a drug target.

Metal-catalyzed cyclopropanation of exo enol ethers results in formation of spiro 5,6-ring systems after subsequent modification. Cyclopropanation of enol ether **142** with ethyl diazoacetate and catalytic copper afforded cyclopropane **156** as a mixture of 4 diastereomers (Scheme 1.42).¹⁰⁷ Cyclopropane **156** was subsequently converted to 5,6 spiroketal **160** through reduction, oxidation, and Lewis acid-induced ring enlargement. LiAlH₄ reduction of cyclopropane **156** led to the corresponding primary alcohol **157**. Oxidation of alcohol **157**

Scheme 1.42



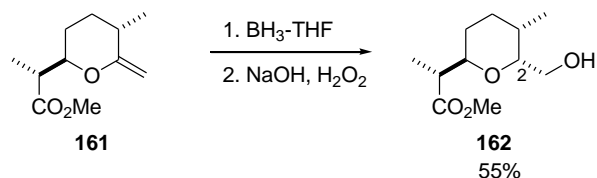
yielded aldehyde **158**, which was treated *in situ* with a Lewis acid catalyst [$\text{Yb}(\text{OTf})_3$] to provide the linear, zwitterionic intermediate **159**. Intramolecular addition of the enolate from the less hindered, top face solely produced spiroketal **160** as the product. This methodology proved to be an effective way to make various 5,6-spiroketal from exo enol ethers via the formation of new carbon-carbon bonds. This study is an important entry towards the manufacture of 5,6-spiroketal, which are functional groups prevalent in many natural products.

Addition of boron to exocyclic enol ethers is a highly versatile addition process. Not only can these boron species be oxidized to primary alcohols, but they can also be used as coupling partners in metal-mediated coupling reactions. Hydroboration and oxidative workup of enol ether **161** resulted in alcohol **162** (55%) (Scheme 1.43).⁵⁵ Tetrahydropyranyl alcohol **162** resulted as the major product because boron approached the tetrahydropyranyl double bond from the opposite face of the adjacent methyl group.

Exocyclic enol ethers are hydroborated and used as coupling partners in Suzuki coupling.¹⁰⁷ This is an effective carbon bond forming process that extends the utility of exocyclic enol ethers. Enol ethers are readily used to couple fragments together, to make larger,

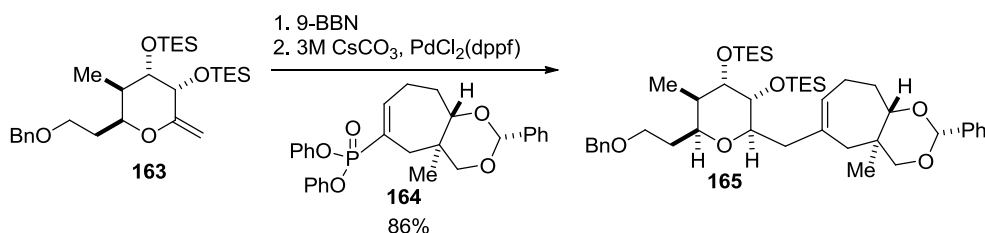
more complex molecules. Thus, the hydroboration and subsequent Suzuki coupling of enol ethers has proven to be a very convergent synthetic process toward natural product synthesis.

Scheme 1.43



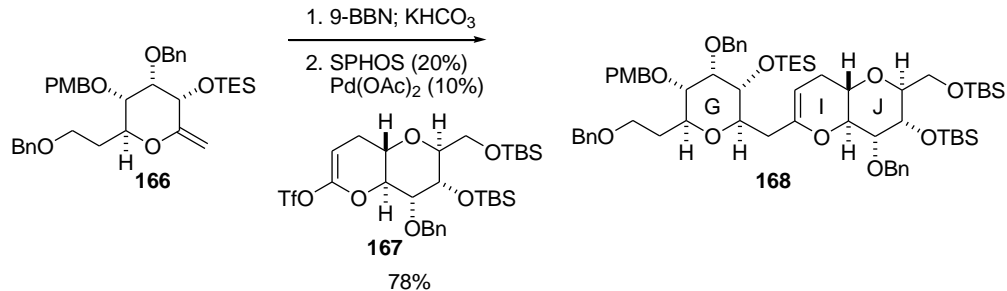
Suzuki-Miyaura cross coupling of an exocyclic enol ether was utilized in the first reported synthesis of brevisin (Scheme 1.44).¹⁰⁸ Hydroboratation of 2-methylenetetrahydropyran **163** with 9-BBN gave the corresponding alkylborane, which was treated with phosphonate **164** in the presence of catalytic palladium and cesium carbonate *in situ* to provide tetrahydropyran **165**. Tetrahydropyranyl intermediate **165** was later carried on to form the ABC ring system of Brevisin.

Scheme 1.44



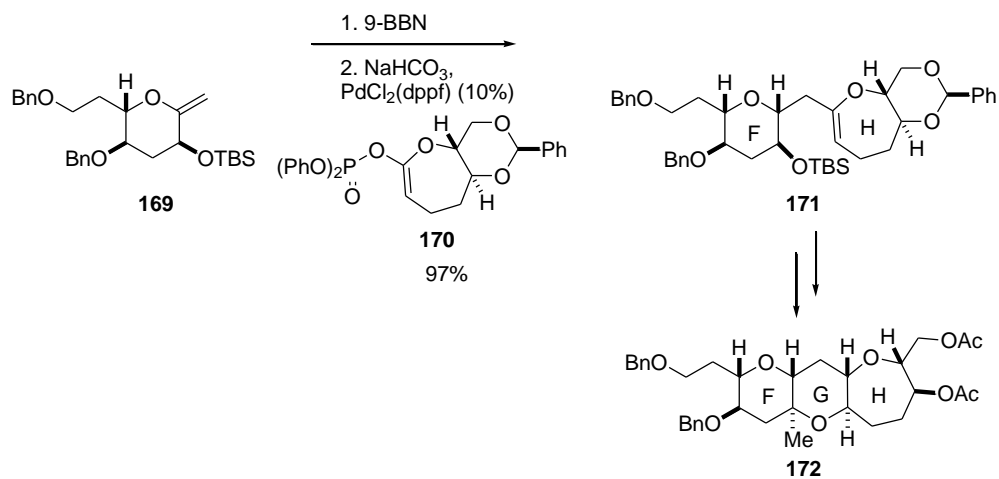
Suzuki coupling of an enol ether to a vinyl triflate was used as a key step in Nicalou's synthesis of the GHIJKLMNO ring domain of maitotoxin (Scheme 1.45).¹⁰⁹ Maitotoxin is a very large secondary metabolite possessing high levels of toxicity.¹¹⁰ Exo enol ether **166** was hydroborated and subsequently coupled to vinyl triflate **167** under palladium catalysis. Suzuki-coupled product **168** was produced, which formed the carbon framework for the GIJ ring system of maitotoxin.

Scheme 1.45



Work towards the manufacture of gambierol has utilized B-alkyl Suzuki coupling of exo enol ethers in the synthetic approach. Gambierol is a marine polyether toxin isolated from dinoflagellate *Gambierdiscus toxicus*.¹¹¹ This tetrahydropyranyl-containing natural product demonstrates toxicity against mice with LD_{50} values of 50 $\mu\text{g}/\text{kg}$. Sasaki et al. stereoselectively synthesized the FGH ring system of this natural product (**172**), using a Suzuki coupling to obtain the required carbon framework (Scheme 1.46).¹¹² Hydroboration of enol ether **169** was

Scheme 1.46



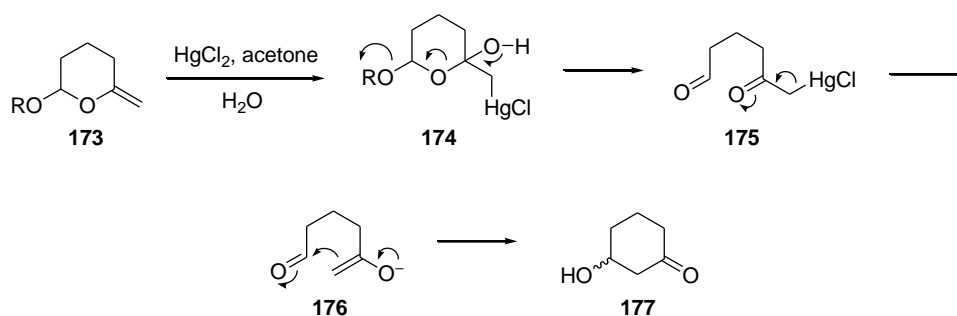
followed by palladium catalyzed addition of enol phosphonate **170** to afford cross coupled-product **171** in excellent yield. Thus, the Suzuki coupling of fragments **169** and **170** successfully formed the cyclization precursor **172** of the FGH ring system of gambierol.

Rearrangements

Enol ethers have been used in several types of rearrangement reactions. Although the reported rearrangements do not directly create new carbon-carbon bonds or couple large carbon fragments together, they serve as methods to make alternative functional groups from 2-methylenetetrahydropyrans. Rearrangements of 2-methylenetetrahydropyrans are used to synthesize functionalized cyclohexanones, cyclohexenes, tetrahydropyrans, and tetrahydrofurans through Ferrier carbocyclic rearrangements, metal catalyzed rearrangement, olefin metathesis, and hydrolysis/rearrangement reactions.

Ferrier carbocyclic rearrangement of exocyclic enol ethers provides substituted cyclohexenones. Ferrier rearrangement involves the coordination of the exo enol ether to a mercury salt, which is followed by ring-opening and ring-closing processes to afford β -ketols. A proposed mechanism for this reaction is shown in Scheme 1.47. Hemiacetal **174** is formed through hydroxymercuration of olefin **173**. Loss of methanol is followed by intramolecular cyclization of diketone intermediate **176** to provide β -hydroxy ketone **177**.

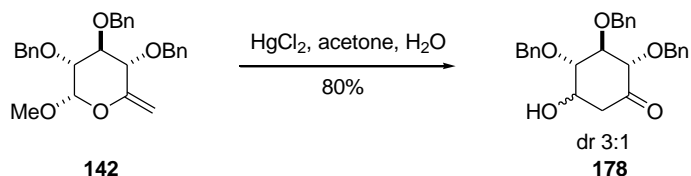
Scheme 1.47



This process was first used toward the manufacture of cyclitols from carbohydrates (Scheme 1.48).¹¹³ Treatment of enol ether **142** with mercury(II) chloride in aqueous acetone afforded cyclohexanone **178** as a mixture of epimeric diastereomers (3:1) in 80% yield. This reaction yielded low diastereoselective formation of the new alcohol chiral center. Elimination

of the β -hydroxyl group to form the corresponding enone avoids the formation of diastereomeric mixtures while maintaining a reactive functionality.

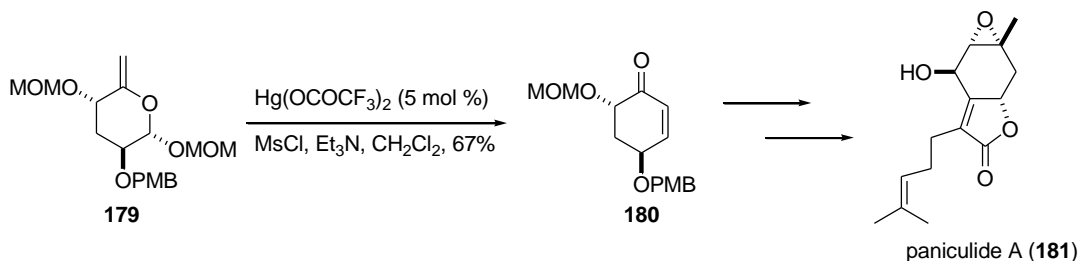
Scheme 1.48



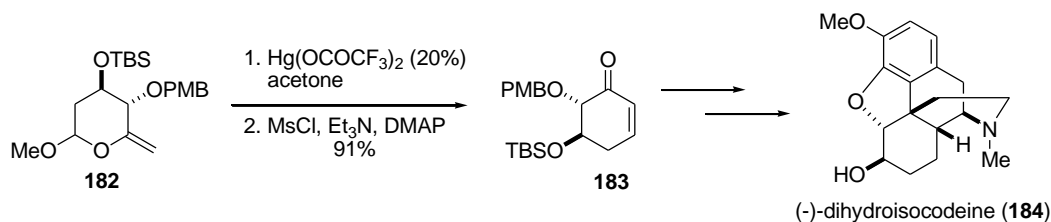
Ferrier carbocyclization followed by β -elimination is used towards the manufacture of α,β -unsaturated cyclohexanones. The transformation of exo enol ethers to enones has been utilized toward the manufacture of bioactive substrates such as PIMs (a glycolipid component of cell walls)¹¹⁴ and aminoglycosides (a large family of molecules with antibiotic activities)¹¹⁵ as well as bioactive natural products. A formal synthesis of paniculide A, a highly oxygenated bisabolene that was isolated from the culture broth of *Andrographis paniculata*,¹¹⁶ involves the formation of enone **180** from exo enol ether **179**. After Ferrier carbocyclization, β -elimination of the intermediary alcohol afforded enone **180**, which was further manipulated to provide a formal synthesis of paniculide A (**181**) (Scheme 1.49).¹¹⁷

Ferrier rearrangement has also been used towards a formal synthesis of (-)-morphine, a well-known pharmaceutical alkaloid isolated from opium poppy (Scheme 1.50).¹¹⁸ Mercury-metal catalyzed cyclization of enol ether **182** followed by mesylation

Scheme 1.49



Scheme 1.50

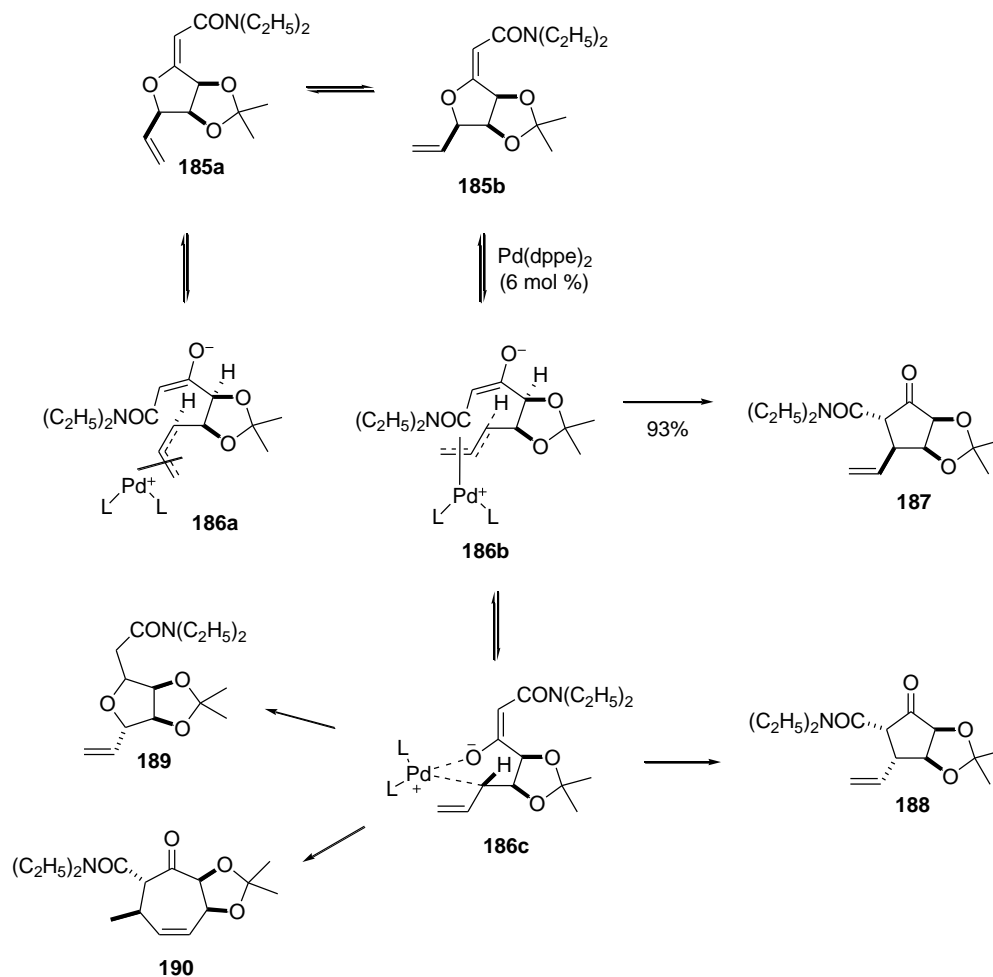


of the newly formed β -hydroxy alcohol yielded cyclohexenone **183**. Enone **183** provided (-)-dihydroisocodeine (**184**), a known morphine precursor,¹¹⁹ after subsequent synthetic manipulations.

Substituted enol ethers have undergone palladium-catalyzed rearrangements. 5-membered exocyclic enol ethers, stabilized by pendant electron-withdrawing groups were converted to cyclopentanone products.¹²⁰ The reaction involves coordination of the palladium catalyst to the pendant vinyl group of stabilized enol ether **185**. Intramolecular, back-side attack of the π -allyl palladium species by the enolate provides the expected stereochemistry at the C_3 position of cyclopentanone **187** (Scheme 1.51).

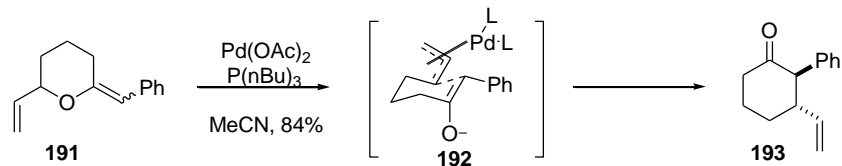
Ionization of **185b** is favored over the ionization of **185a** due to unfavorable eclipsing interactions associated with complex **186a**. Therefore ionization of **185b** leads to the more favorable intermediate **186b** with an inversion of the stereochemistry. At this point palladium-allyl complex **186b** can either undergo bond rotations to form compounds **188**, **189**, and **190** via complex **186c** or ring closure to afford cyclopentanone **187**. Since enolate addition to the palladium complex is faster than syn-anti conversions, production of cyclopentanone **187** predominates.

Scheme 1.51



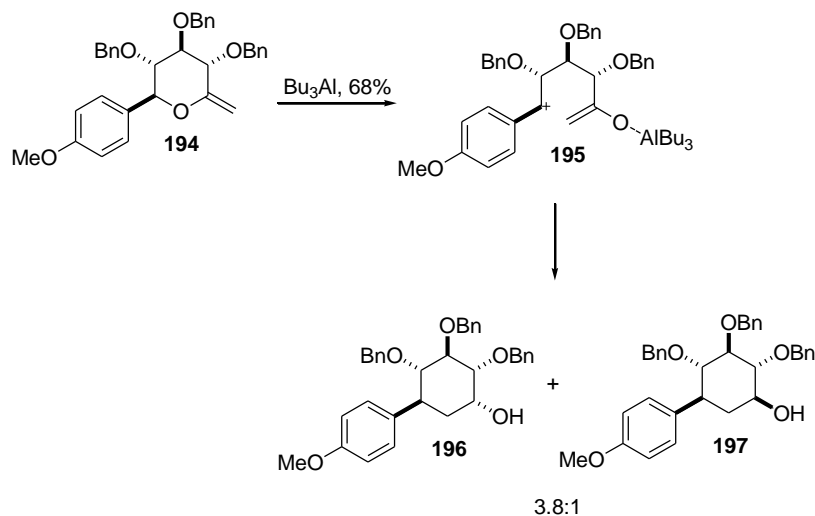
More recently, 6-membered enol ethers have been employed in this reaction (Scheme 1.52).¹²¹ Cyclohexanone **193** was prepared stereoselectively from exocyclic enol ethers using palladium acetate (10 mol%) and tributyl phosphine via a [1,3]-O-to-C rearrangement. The observed *trans*-relative stereochemistry arises from chair transition state **192** where the phenyl and allyl groups are held in equatorial positions.

Scheme 1.52



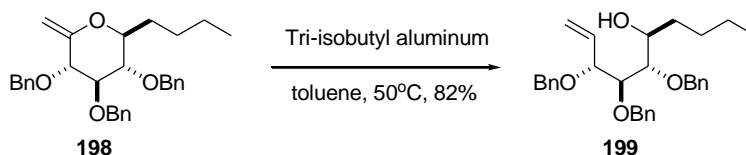
Exocyclic enol ethers containing electron-withdrawing groups at the C₆ position have been cyclized using Lewis acids to form hydroxy-cyclohexanes. Alcohols **196** and **197** are formed as a diastereomeric mixture from enol ether **194** (Scheme 1.53).¹²² This reaction occurs

Scheme 1.53



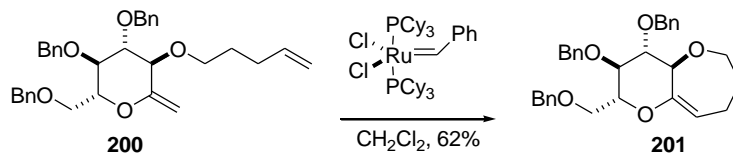
by transposition of the exocyclic carbon atom with the enol ether oxygen followed by hydride delivery to afford the cyclohexanyl products with retention of stereochemistry. By a similar process, enol ethers can also be converted to linear alcohols. Enol ether **198** was hydroaluminated and subsequently eliminated to yield alcohol **199** using tri-isobutyl aluminum (Scheme 1.54).¹²³

Scheme 1.54



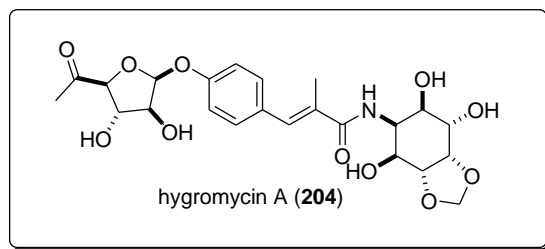
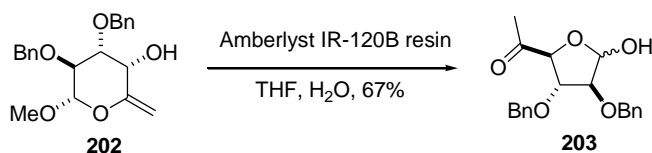
Ring closing metathesis of exocyclic enol ethers using Grubbs first generation catalyst yields fused ether ring systems like **201** from corresponding dienes **200** (Scheme 1.55).¹²⁴ This methodology, is very effective at synthesizing 7 and 8-membered rings, which otherwise are difficult to access.

Scheme 1.55



Exo enol ethers containing C₃ alcohols can undergo rearrangement to the corresponding keto-tetrahydrofurans (Scheme 1.56).¹²⁵ Enol ether **202**, after subjection to acidic conditions, produced furanose **203** as an anomeric mixture via hydrolysis and subsequent rearrangement. This ring contraction was effective in manufacturing a precursor toward the synthesis of hygromycin A (**204**).

Scheme 1.56



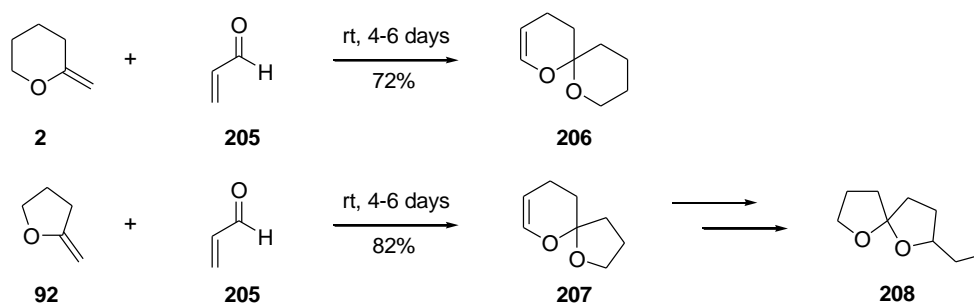
Pericyclic Reactions

Exocyclic enol ethers are used as partners in pericyclic reactions such as the Hetero-Diels Alder, Povarov, [3+2], and 1,3 dipolar cycloadditions. These carbon bond-forming processes are

principally used toward spiroketal synthesis. Claisen rearrangements of exo enol ethers have also been reported and are effective methods toward the manufacture of dihydropyrans and cyclooctanes.

The Inverse electron demand Hetero-Diels-Alder reaction of exo enol ethers is effective for the production of spirocyclic tetrahydropyrans. These subunits are present in a variety of polyether antibiotics and their analogs. Ireland first described the use of 2-methylene tetrahydropyrans **2** and tetrahydrofurans **92** as dienophile substrates.¹²⁶ The cycloaddition of these enol ethers with acrolein **205** yielded the corresponding spiroketals **206** and **207** in good yields (Scheme 1.57). Use of heat or Lewis acid catalysis in this reaction rapidly led to isomerization of the exo enol ethers to the endocyclic enol ethers, however, reaction at room temperature over a number of days with 1 mol % hydroquinone yielded the desired spiroketals **206** and **207** in large scale. Oxidative ring contraction of spiroketal **207** and successive manipulations yielded racemic chalcogran **208**, the principal aggregation pharmane of the L. chalcographus beetle, a known pest of the Norway spruce.

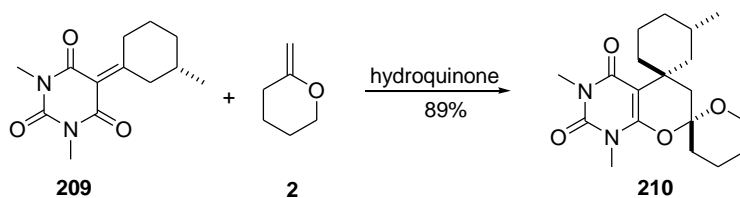
Scheme 1.57



The Hetero-Diels-Alder reaction of exo enol ethers has been well utilized in the literature because it is an effective method for stereoselective spiroketal synthesis that tolerates a variety of different dienes, including those that are hindered. Palasz demonstrated that many hindered dienes work well in this reaction, and the application of diene **209** to the Diels-Alder reaction

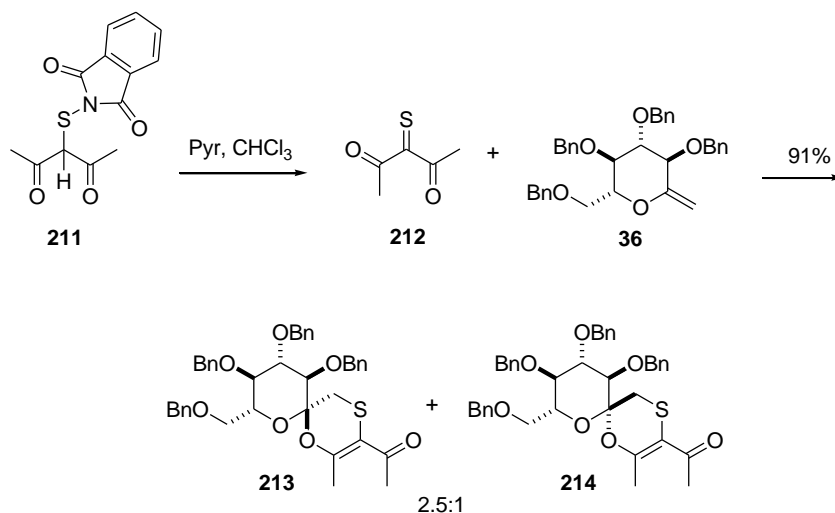
proved interesting because two spiro centers could be stereoselectively made in one step (Scheme 1.58).¹²⁷ One diastereomer was isolated in 89% yield, however the stereochemistry of that product could not be identified. Fused uracil-spirotetrahydropyranyl products like **210** were manufactured because they are reported to have a wide range of biological properties and are otherwise challenging to synthesize.

Scheme 1.58



Hetero-Diels-Alder reactions have also been performed on sulfur-containing dienes. The reaction of *exo*-glycal **36** with diketone **212** resulted in spiroketals **213** and **214** as a 2.5 to 1 mixture of diastereomers (Scheme 1.59).¹²⁸ Pyridine was used to form the intermediate **212** from diketone **211** *in-situ*. This diene was then reacted with *exo* enol ether **36** to yield the inverse-electron demand hetero-Diels Alder products.

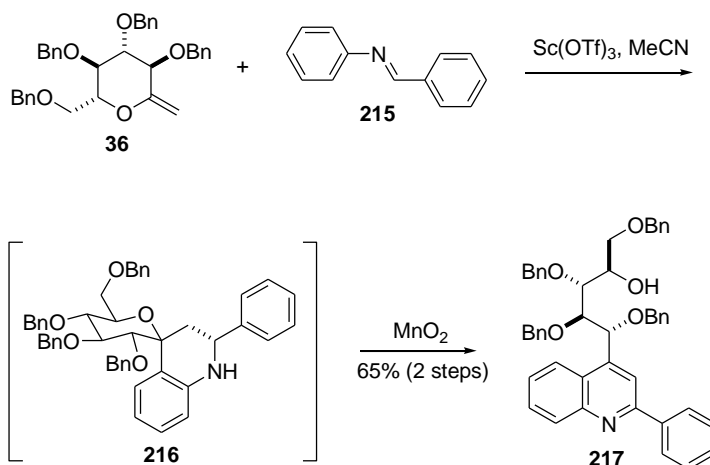
Scheme 1.59



Exo enol ethers can also be used as partners in the Povarov reaction, which is a [4+2] cycloaddition between an aromatic Schiff base and an activated olefin.¹²⁹ The Povarov reaction of exo enol ethers was used to synthesize sugar-quinoline adducts that could potentially have high biological activity. The sugar portion could facilitate drug delivery and aid in DNA intercalation of the quinoline ring. The Povarov reaction between exo-glycal **36** and imine **215**, under Lewis acid conditions, provided spiro-intermediate **216** (Scheme 1.60).¹³⁰ Subsequent oxidation with manganese oxide resulted in cleavage of the spiro-ring and forms quinoline **217**. This process was driven by the aromatization of the tetrahydroquinoline portion of intermediate **216**.

Synthetic efforts towards the rubromycins was performed using a [3+2] cycloaddition of exo enol ethers and a β -hydroxy enone. The rubromycins represent an interesting class of

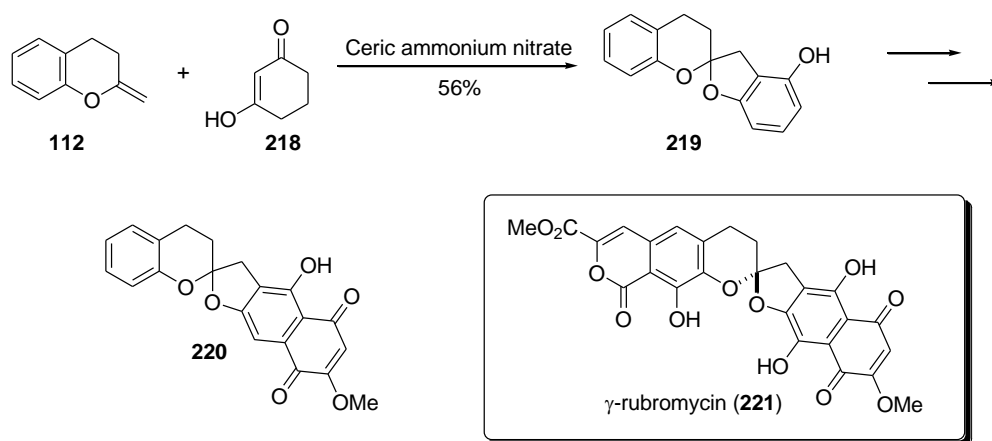
Scheme 1.60



bioactive spiroketal natural products that are found to inhibit Gram-positive bacteria.¹³¹ The Pettus group employed the cyclization of dihydrocoumarin-derived enol ether **112** and β -hydroxy enone **218** towards a model system study of the rubromycins (Scheme 1.61).¹³² A zwitterion is formed from enone **218**, which successively adds to enol ether **112** via a [3+2]

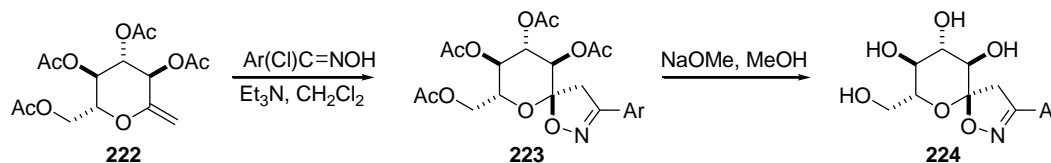
cycloaddition to provide spiroketal **219** with no mention of diastereoselectivity. Further elaboration of spiroketal **219** provided naphthoquinone **220**, which completed the model-system study for γ -rubromycin (**221**).

Scheme 1.61



The [1,3]-dipolar cycloaddition is a synthetically useful method toward carbon-carbon bond formation. This cycloaddition has been applied to exo enol ethers toward the formation of spiroisoxazolines, which are biologically active substrates. Spiroisoxazolines **223** were made from exo-glycal **222** through a [1,3]-dipolar cycloaddition with aryl nitride oxides (Table 1.4).¹³³

*Table 1.4: [1,3]-Dipolar Cycloaddition of Enol Ether **222***

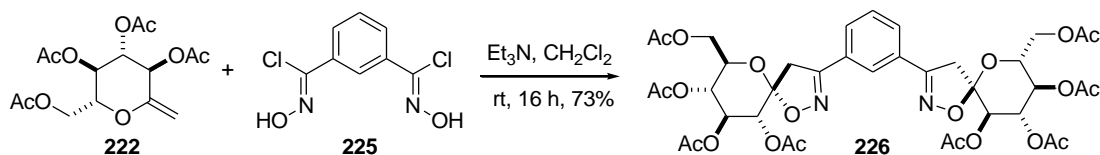


Entry	Ar	Yield of 224 (%)	Yield of 225 (%)	K_i of 225 (μM)
1	p-MeO-Ph	83	98	6.6
2	p-Me-Ph	95	93	7.9
3	Ph	99	97	19.6
4	p-NO ₂ -Ph	94	99	92.5
5	2-Naphthyl	94	78	1.7

The anomerically stabilized spiroisoxazoline isomers were exclusively produced in excellent yields. Deprotection of the alcohols yielded triols **224**, which were subsequently evaluated for their biological activity against glycogen phosphorylase. Inhibitors of glycogen phosphorylase are possible drug candidates toward glycemic control in type-2 diabetes. The biological activity was measured by K_i values, and the 2-naphthyl derivative was found to have very high inhibitory effects toward glycogen phosphorylase, making it a likely drug candidate (entry 5, Table 1.4).

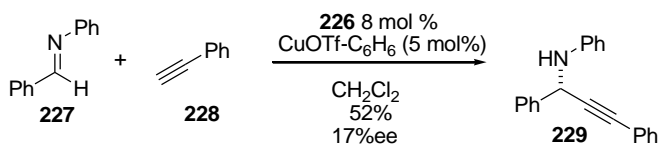
The [1,3] dipolar cycloaddition of bis-arylnitrile oxides have also been reported to form bi-directional bis-spiroketal adducts for use as possible ligands in enantioselective catalyzed reactions (Scheme 1.62).¹³⁴ Two equivalents of enol ether **222** were combined with bis-arylnitrile oxide **225** to provide bis-isoxazoline **226** as one diastereomer. A pyridine version of

Scheme 1.62



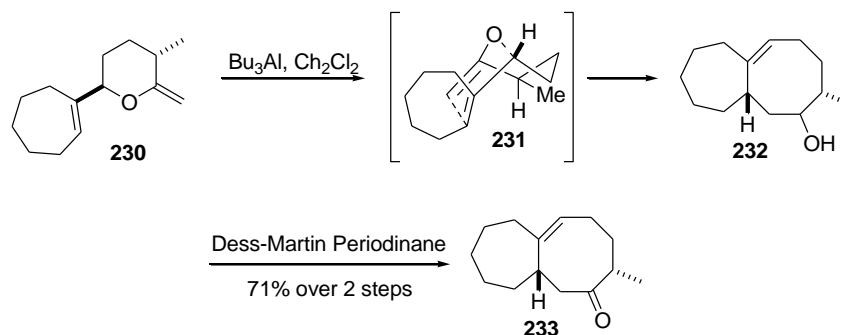
the bis-isoxazoline was successfully synthesized as well, in 71% yield. Application of bis-isoxazoline **226** as a ligand in the Cu(I)-catalyzed imine alkynylation reaction of imine **227** with phenyl acetylene **228** provided the desired alkyne products, but with poor enantioselectivity (Scheme 1.63).

Scheme 1.63



Claisen rearrangements have been performed on olefin-containing enol ethers to form cyclooctenes (Scheme 1.64). This [3,3] sigmatropic rearrangement proceeds under Lewis acid

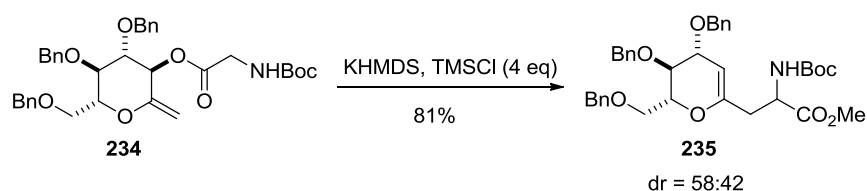
Scheme 1.64



catalysis,¹³⁵ upon heating,¹³⁶ or by microwave irradiation.¹³⁷ This method was used to form the 7-8 fused ring system in micrandilactone A when ring-closing metathesis proved unsuccessful. Lewis acid addition to exo enol ether **230** yielded 7-8 ring system **232** as a single diastereomer after undergoing chair-like transition state **231**. Subsequent oxidation of alcohol **232** yielded ketone **233** in 71% over two steps.

Claisen-Ireland rearrangements have been carried out using sugar derivatives (Scheme 1.65).¹³⁸ Exocyclic enol ether **234** was transformed under basic conditions to enol ether **235** with little diastereoselectivity. This served as a method for the construction of β -C-glycosides.

Scheme 1.65

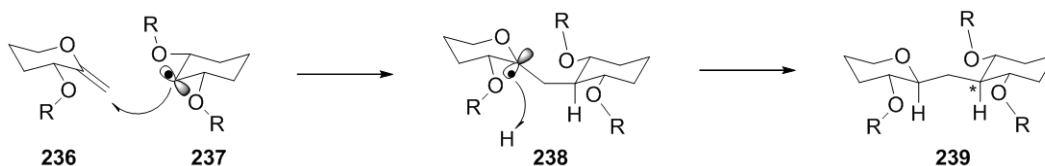


Radical Reactions

Exocyclic enol ethers can react with radicals to give sulfides and create carbon-carbon bonds in a synthetically convergent manner. Typically, radical donors **237** react with an enol

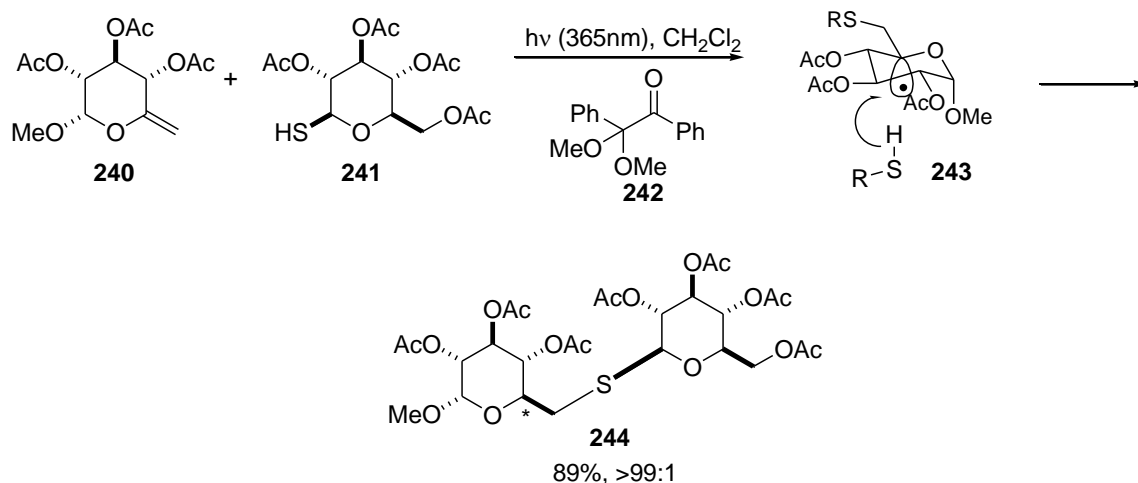
ether **236** to form anomeric radicals **238**. The anomeric radical will perform an axial capture of a hydrogen to yield diastereoselective tetrahydropyranyl products at that center (Scheme 1.66).¹³⁹ The stereochemical outcome of the newly formed radical donor stereocenter is not always as straightforward.

Scheme 1.66



The coupling of exocyclic enol ethers to thiols has been reported using a radical process. This chemistry was used to manufacture carbohydrate mimics for biological studies and leads for new therapeutics. Exo enol ethers were coupled to anomeric sugar thiols **241** (Scheme 1.67).¹⁴⁰

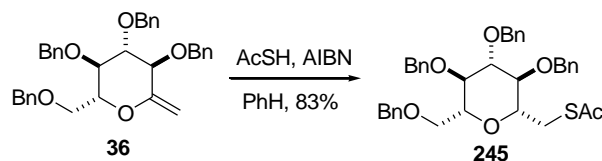
Scheme 1.67



This light-induced radical reaction, utilizing 2,2-dimethoxy-2-phenylacetophenone (**242**) as photoinitiator, provided 1,6-linked S-disaccharide **243** in good yield with high diastereoselectivity at the newly formed anomeric carbon. Addition of thiol **241** to exo-glycal **240** resulted in formation of radical intermediate **243**. Addition of hydrogen from the less hindered, bottom face of the intermediate is favorable, producing diastereomer **244**.

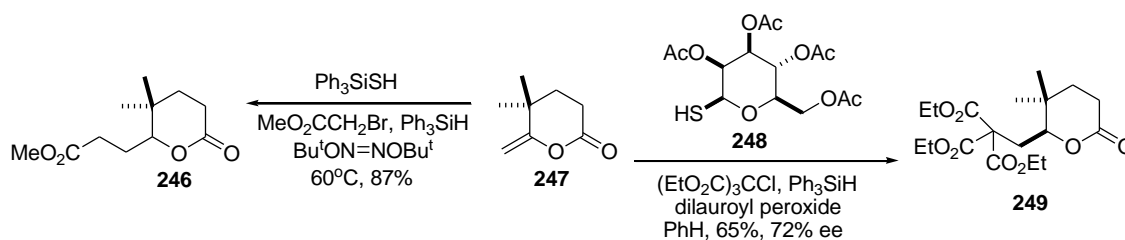
The coupling of thiols to enol ethers has also been reported by AIBN initiation. Exocyclic glycol **36** and thiolacetate produced thiolacetate **245** (Scheme 1.68).¹⁴¹ Tetrahydropyran **245** was exclusively isolated as one isomer, based on the previously described steric argument.

Scheme 1.68



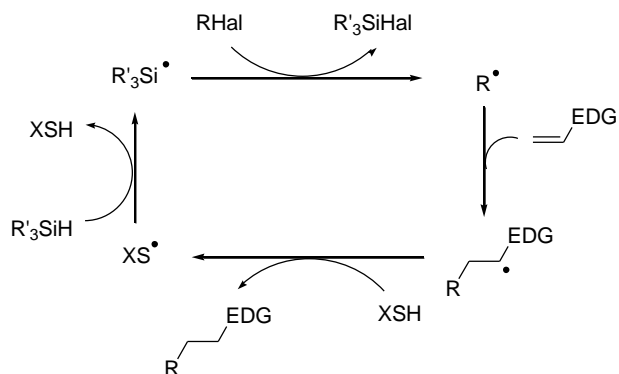
Exocyclic enol lactones have been transformed into alkylated lactones through reactions mediated by triphenylsilane and thiol catalysts (Scheme 1.69).¹⁴² Racemic products were produced with triphenylsilanethiol as the catalyst (5 mole %) and di-^tbutyl hyponitrate acting as the radical initiator. Stereoselective products were created with chiral catalyst **248** (10 mol%) and radical initiator dilauroyl peroxide.

Scheme 1.69



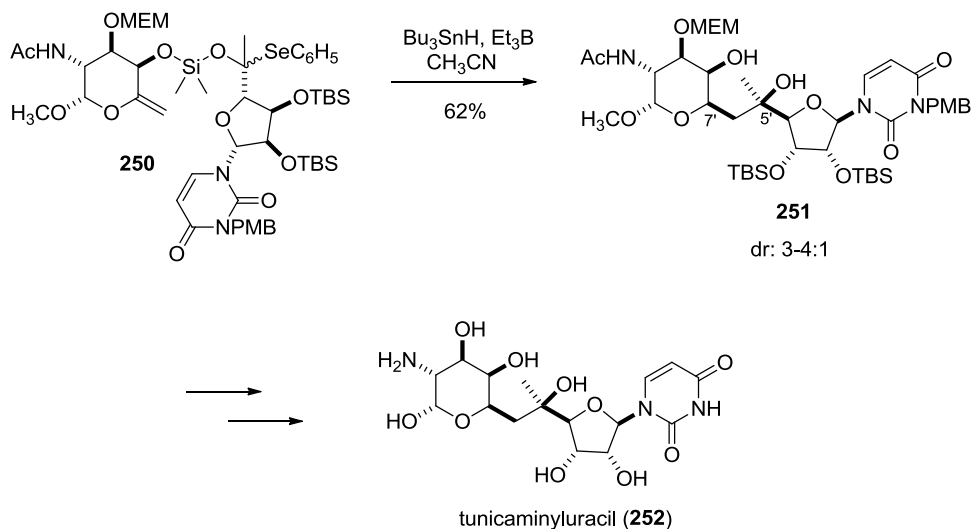
The proposed propagation cycle is outlined in Scheme 1.70. The ^tbutyloxy radical abstracts a hydrogen from triphenylsilane to produce a chain-carrying silyl radical. Abstraction of a halide by the silyl radical produces an intermediate that adds to an electron-rich alkene. Subsequent hydrogen abstraction from a thiol produces the alkene addition product and a sulfide radical. The sulfide radical then facilitates manufacture of the initial silyl catalyst. Absence of the thiol catalyst caused little to no product formation.

Scheme 1.70



Intramolecular radical addition has been facilitated by silane tethers to make carbon-carbon bonds. The use of a silane tether aids in the formation of the new carbon-carbon bond because the reaction proceeds through an intramolecular process rather than an unfavorable intermolecular nucleophilic addition. Myers reported this methodology in the synthesis of the antibiotic tunicamyluracil (**252**) (Scheme 1.71).¹⁴³ The carbon-selenium bond of enol ether **250** underwent radical cleavage. Subsequent addition of the carbon radical to the enol ether

Scheme 1.71

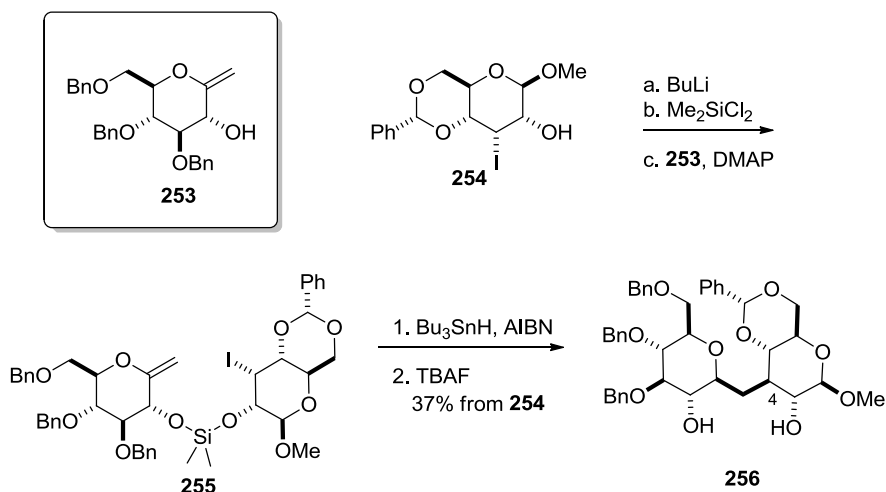


provided tetrahydropyran **251** after axial, anomeric hydrogen capture. C_5' stereocenter formation was controlled by the reaction solvent system. Toluene provided the undesired C_5' diastereomer,

while acetonitrile solvent produced tetrahydropyran **251** in 62% yield. Successive deprotection of the amine and hydroxyl functional groups rendered tunicaminyuracil. This sequence proved to be a highly convergent method for natural product synthesis.

Silyl tethers have been similarly used towards disaccharide synthesis. This cyclization reaction was used to manufacture bioactive disaccharides (Scheme 1.72).¹⁴⁴ In this transition, an alkyl iodide is used as a progenitor of a radical donor. Alcohol **254** is coupled to enol ether **253** through a silyl tether. A 8-*endo-trig* cyclization is mediated by tributyltinhydride to form tetrahydropyran **256**, in 37% yield from iodide **254**, after de-tethering. The stereochemistry of the C₄ stereocenter is expected on a steric basis because cyclohexyl and non-anomeric hexopyranosyl radicals prefer equatorial addition when there are adjacent equatorial substituents.¹⁴⁵

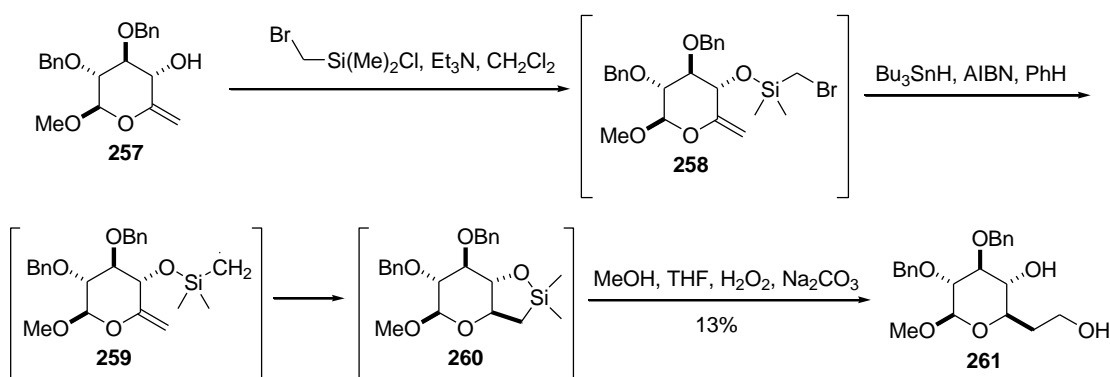
Scheme 1.72



Silyl-tethered radical processes have been used towards β -hydroxy tetrahydropyran synthesis.¹⁴⁶ Enol ether **257** was converted to Diol **261**, albeit in low yield, through hydrohydroxymethylation, a process initially applied to allylic alcohols by Nishiyama¹⁴⁷ and Stork,¹⁴⁸ (Scheme 1.73). Hydroxy-exo enol ether **257** is transformed into silyl ether **258** and

subsequently treated with tributylstannane to yield intermediate **259**. The silylmethylene radical successively cyclizes to the 5-membered siloxy ring **260**. Tetrahydropyranyl diol **261** resulted from oxidative cleavage via a Tamao-Kumada process.¹⁴⁹

Scheme 1.73

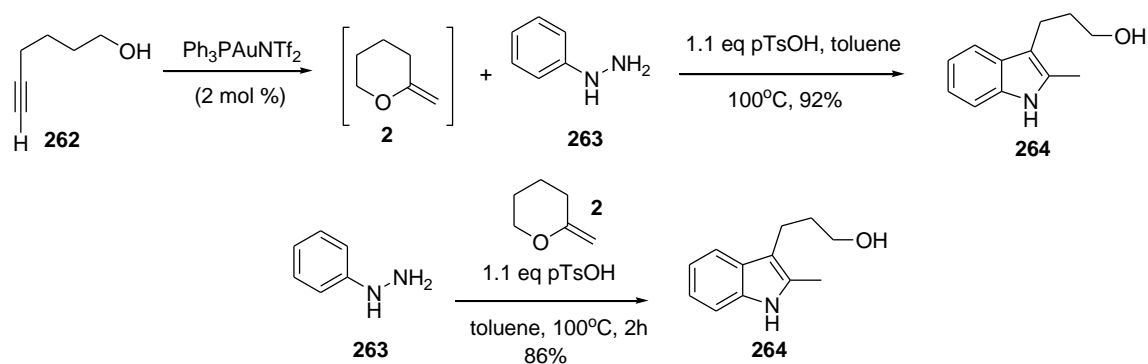


Use as Electrophiles

Amongst the uses of exocyclic enol ethers is their role as electrophiles. Nitrogen and oxygen nucleophilic additions occur at the anomeric carbon of exocyclic enol ethers. Both indole and ketal products have been synthesized by this method. The manufacture of these functional groups is important toward the synthesis of biologically active substrates.

Exocyclic enol ethers are assumed to be intermediates in the hydrohydrazination-Fisher indolization tandem reaction of arylhydrazines with acetylenic alcohols (Scheme 1.74).¹⁵⁰ A general method for the fabrication of these moieties is important towards the synthesis of indole-based pharmaceuticals like serotonin, indomethacin, and sumitriptan. The mechanism of this hydrohydrazination-Fisher indolization proceeds through an exo-enol ether intermediate. This reaction pathway is confirmed by using the corresponding exo enol ethers as reaction components rather than acetylenic alcohols.

Scheme 1.74



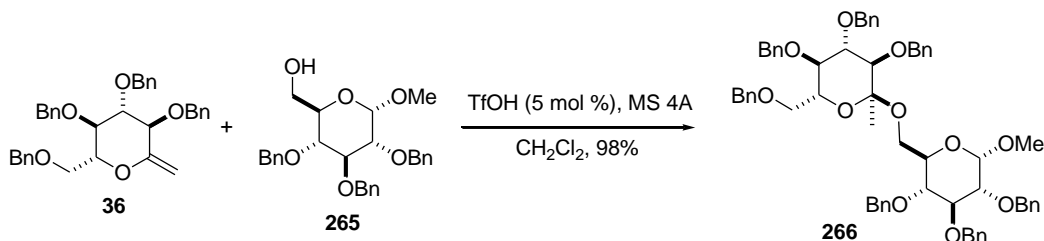
Acetylenic alcohol **262** forms a complex with a gold catalyst, which is subsequently cyclized, resulting in *in-situ* exo enol ether formation. Nucleophilic addition of hydrazine **263** to the enol ether intermediate is followed by *p*-toluenesulfonic acid induced hydration and subsequent Fisher indolization to yield indole **264**. This nucleophilic addition of hydrazine demonstrates the use of exocyclic enol ethers as electrophiles for nitrogen addition.

To determine the plausibility of an exocyclic enol ether intermediate, 2-methylenetetrahydropyran **2** was subjected to only Fisher-indolization conditions. Addition of hydrazine **263** to enol ether **2** produced indole **264**. The creation of the same indole product from either addition of an exo enol ether or acetylenic alcohol indicates that the exo enol ether is indeed the Fisher-indolization precursor in this reaction, whether it is added directly or made *in-situ*. By using acetylenic alcohols as reactants, the enol ether is made and used within the reaction, circumventing the need for isolation of this labile product.

Exo enol ethers have been coupled with numerous alcohols through nucleophilic addition to the anomeric center. In particular, enol ethers have been used for carbohydrate synthesis. The synthesis of carbohydrates and carbohydrate analogs is important because they are biologically active components that mediate cell-cell recognition and moderate behavior of enzymes. Glucose, galactose, and mannose-derived disaccharides have been synthesized by the *O*-

glycosidations of exo-glycals with protected glycosides (Scheme 1.75).¹⁵¹ Exclusive formation of the *O*-glycosylation product **266** results from combining exo-glycal **36** with alcohol **265** under acid catalyzed conditions. Under these thermodynamic conditions, the β -glucoside **266** is formed preferentially.

Scheme 1.75



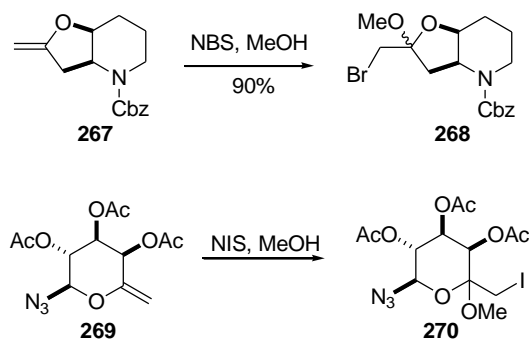
Use as Nucleophiles

Exo enol ethers have developed as effective nucleophiles and are similar in their reactivity to alkenes. Nucleophilic reactions of the exo olefin include the formation of halonium ions that are successively opened by secondary nucleophile addition and protic or Lewis acid hydrolysis. Less common is the use of exocyclic enol ethers in nucleophilic carbon-carbon bond formation. Examples of these types of transformations include exo-glycal dimerization and addition to an episulfonium ion.

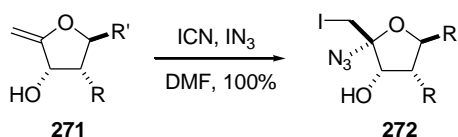
Nucleophilic attack of an electrophilic halogen species by an exo enol ether produces intermediate halonium ions, which undergo nucleophilic attack to yield enol ether addition products. Bromoetherification¹⁵² or iodoetherification¹⁵³ of exo enol ethers **267** and **269** formed racemic ketals **268** and **270** (Scheme 1.76). Similarly, secondary nucleophilic attack of an iodonium ion by azide resulted in the formation of iodide **272** with high levels of regio and stereoselectivity (Scheme 1.77).¹⁵⁴ The observed stereoselectivity is due to preferential iodonium ion formation on the β -face of the molecule. In the absence of the C₃ hydroxy group,

no selectivity was observed. Other conditions used to manufacture iodides from exo enol ethers include NaNH_3 , I_2 , and $[\text{Bn}(\text{Et})_3\text{N}]\text{Cl}$,¹⁵⁵ I_2 , MeCN ,¹⁵⁶ and NIS , H_2O .¹⁵⁷

Scheme 1.76

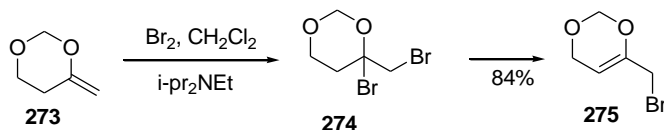


Scheme 1.77



Elimination of halides formed from exo enol ethers yields haloalkenes. Bromination of enol ether **273** in the presence of Hunig's base produced allyl bromo-enol ether **275** (Scheme 1.78).¹⁵⁸ Formation of dibromide intermediate **274** was followed by β -elimination of the tertiary bromide to provide bromide **275**. The more stable, internal olefin is produced rather than the exocyclic olefin.

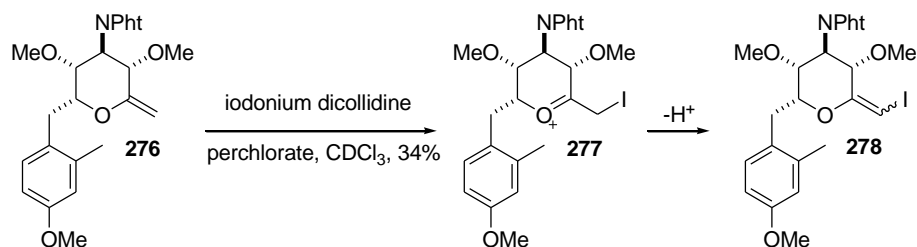
Scheme 1.78



Iodo-enol ethers can also be synthesized through the nucleophilic attack of a halogen by an exo enol ether followed by elimination (Scheme 1.79). Iodonium intermediate **277** is directly eliminated as compared to the secondary bromide addition and subsequent elimination of

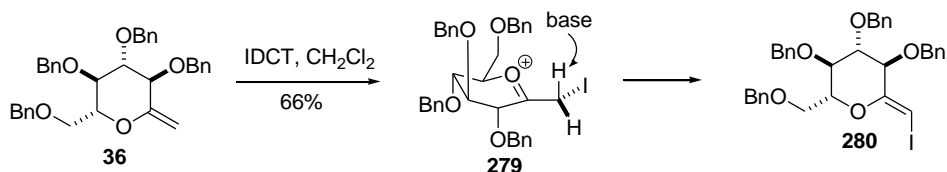
dibromide **274**. Treatment of enol ether **276** with iodonium dicollidine perchlorate leads to oxonium ion intermediate **277**. Elimination of a proton from the exocyclic carbon provided iodoenol ether **278** as a mixture of stereoisomers in low yield.

Scheme 1.79



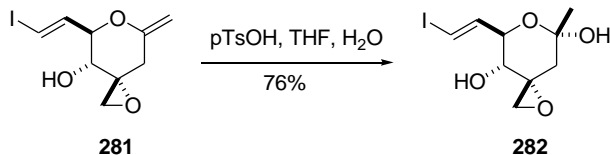
Halo-enol ethers can be prepared by selective iodonium addition/elimination of exo enol ethers using iodonium dicollidinium triflate (Scheme 1.80).¹⁵⁹ Exo-glycal **36** is transformed into iodo enol ether **280** through elimination of oxonium intermediate **279**. Stereoselectivity is derived from the conformational preference of the intermediate oxonium ion **279**. Abstraction of a proton that is aligned parallel to the oxonium ion pi bonds then provides halo enol ether **280**. This proves to be an effective method for synthesizing iodo-enol ether substrates stereoselectively from the corresponding sugar derivatives. Iodo-enol ethers are used as partners in Sonogoshira,¹⁶⁰ Suzuki,¹⁵⁹ and Stille¹⁶¹ cross coupling reactions.

Scheme 1.80



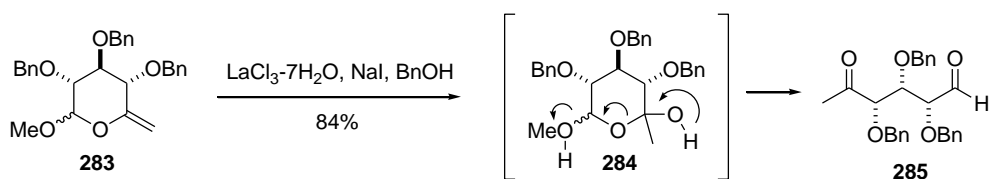
Addition of water to exocyclic enol ether nucleophiles can be effected under both protic and Lewis acid conditions to yield both hemiketals and keto-products. Treatment of enol ether **281** with *p*-toluenesulfonic acid provided the expected Markovnikov product **282** (Scheme 1.81).¹⁶² Subjection of *exo*-glycal **283** with a lanthanum reagent system led to ring-opened

Scheme 1.81



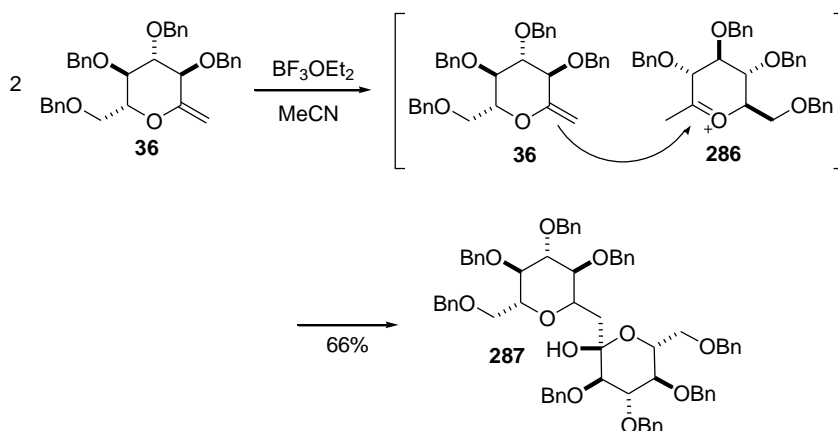
product **285** (Scheme 1.82).¹⁶³ Hydration of the exocyclic double bond was followed by successive ring opening of hemiketal **284**. Hemiketal cleavage proceeds with concomitant loss of methanol to provide keto-aldehyde **285**.

Scheme 1.82



The use of exocyclic enol ethers as nucleophiles in carbon-carbon bond forming reactions is limited. Dimerization of exoglycal **36** in the presence of a Lewis acid provided bis-tetrahydropyran **287** (Scheme 1.83).¹⁶⁴ In this reaction one molecule of the enol ether is acting

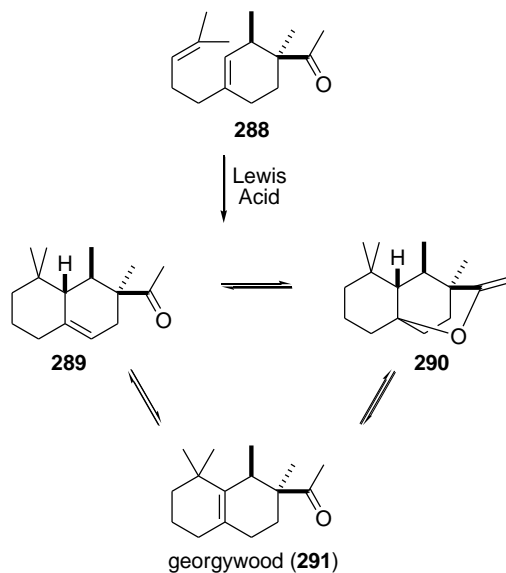
Scheme 1.83



as a nucleophile while the other is an electrophile. One equivalent of exocyclic enol ether **36** attacks oxonium species **286** formed *in-situ* from another molecule of the enol ether **36** and the

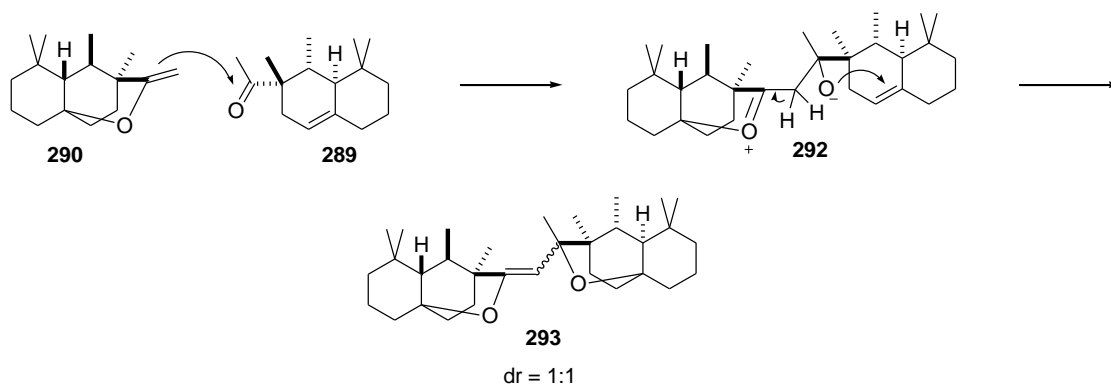
Lewis acid. Water workup leads to the anomeric dimer **287**. Schroder's group detected exo enol ether dimerization products in their research of acid-promoted 1,5-diene cyclizations.¹⁶⁵ A mixture of isomers **289**, **290**, and **291** resulted upon subjection of pseudo-georgywood (**288**) to Lewis acidic conditions (Scheme 1.84). Typically the isomer mixture was converted to the most

Scheme 1.84



stable constituent, georgywood (**291**), through addition of catalytic *p*-toluenesulfonic acid. However, upon standing at room temperature for several weeks the product mixture also produces dimer **293** as a crystalline solid (Scheme 1.85). Addition of enol ether **290** to ketone

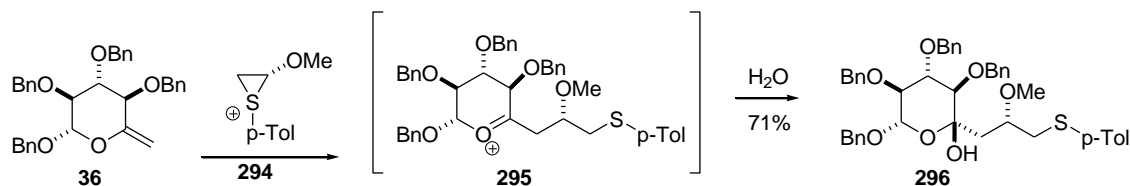
Scheme 1.85



289 results in formation of oxonium ion intermediate **292**. Subsequent elimination and cyclization generates dimer **293** as a 1:1 mixture of E:Z stereoisomers.

The Smoliakova research group demonstrated the nucleophilic properties of *exo*-glycals for the preparation of β -C-glycosides.¹⁶⁶ Nucleophilic addition of Exo-glycal **36** to episulfonium ion **294** yields oxonium ion **295** (Scheme 1.86). Intermediate **295** was quenched with water to

Scheme 1.86



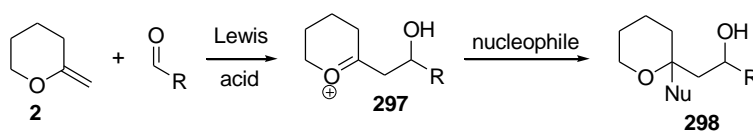
provide hemiketal **296**. Other external nucleophiles used in this process included methanol and sodium cyanoborohydride. The observed stereoselectivity of the secondary nucleophilic addition is based upon steric and electronic factors.¹⁶⁷ Nucleophilic addition occurs from the face opposite that of the C₆ substituent to afford the anomERICALLY-stabalized thermodynamic product. This example of *exo*-glycal nucleophilic addition to episulfonium ions demonstrates exocyclic enol ethers as viable nucleophiles when added to activated, electrophilic systems. The resulting products formed are β -oxygenated tetrahydropyrans, which are useful functional groups toward tetrahydropyranyl natural product synthesis.

With the exception of the dimerization and Smoliakova examples, the research utilizing exocyclic enol ethers as carbon-carbon nucleophiles is nearly non-existent. The research in our group is geared toward showcasing these nucleophilic nature of exocyclic olefins, namely in carbon-carbon bond forming reactions. The research method involves the synthesis of β -hydroxytetrahydropyrans and dihydropyrans through coupling of 2-methylenetetrahydropyrans with aldehydes and ketones. Not only do these reactions demonstrate the use of *exo* enol ethers

as nucleophiles, but the products produced could also be used as key tetrahydropyranyl ketide intermediates in natural product synthesis.

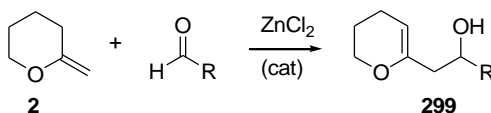
Two different reactions were studied in order to demonstrate the nucleophilic character of exo enol ethers and their ability to create new carbon bonds: three component coupling (Scheme 1.87) and carbonyl-ene reactions (Scheme 1.86) of 2-methylenetetrahydropyrans. The three-component coupling reaction involves formation of oxonium ion intermediate **297** after nucleophilic attack of the enol ether to an activated aldehyde or ketone. Secondary nucleophile trapping of oxonium ion **297** provided β -hydroxy tetrahydropyrans **298** as diastereomeric mixtures in good yield.

Scheme 1.87



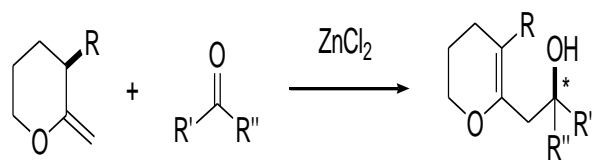
Use of exo enol ethers in the carbonyl ene reaction provided dihydropyrans **299** in excellent yields (Scheme 1.88). Activation of aldehydes and ketones by catalytic zinc(II)

Scheme 1.88

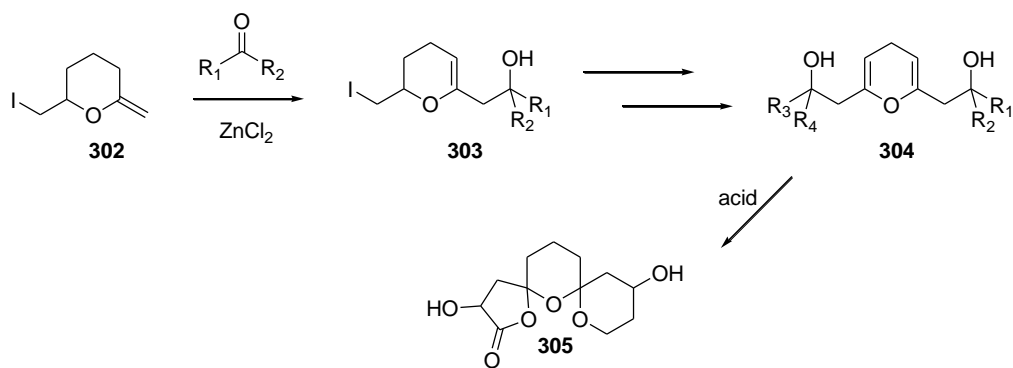


chloride (5-20 mol %) and subsequent addition to exo enol ethers produced racemic mixtures of β -hydroxy dihydropyrans. Chiral induction studies have been performed as an extension of this carbonyl-ene reaction. Through examination of chiral exo enol ethers, preferential stereoisomer formation can be determined (Scheme 1.89). Bi-directional studies were also carried out to assess if bis- β -hydroxypyrans **304** and trioxadispiroketal **305** could be manufactured from the carbonyl-ene methodology (Scheme 1.90).

Scheme 1.89



Scheme 1.90



1.4 References

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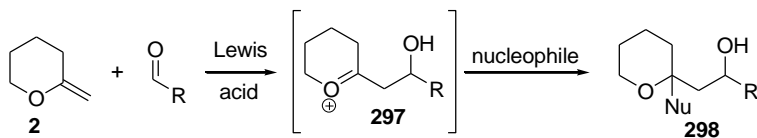
Chapter 2: Three-Component Coupling Reactions of 2-Methylenetetrahydropyrans

2.1 Overview

Tetrahydropyranyl ketides are present in biologically active natural products. Therefore, new methodologies toward the synthesis of tetrahydropyrans and their analogs are synthetically significant. Our synthetic efforts toward β -hydroxy tetrahydropyrans include the use of exo enol ethers as neutral nucleophiles in a three component coupling reaction (Scheme 2.1). General methods utilizing exocyclic enol ethers as nucleophiles have not been published outside of our reports. Endo enol ethers have been more extensively studied as nucleophiles in carbon-carbon bond-forming reactions and lend argument to the use of enol ethers as neutral nucleophiles. This chapter reviews the use of endocyclic enol ethers as nucleophiles in coupling reactions and discusses the development of our three-component coupling reaction of exocyclic enol ethers.

The three component coupling reaction between 2-methylenetetrahydropyrans **2** and aldehydes or ketones occurs under Lewis acid activation (Scheme 2.1). β -Hydroxy-tetrahydropyrans **298** are produced through addition of nucleophiles to oxonium ion intermediates **297**. This reaction demonstrates the nucleophilic nature of exocyclic enol ethers. Reaction conditions that were screened for this process include use of alternative Lewis acids, variation of the reaction stoichiometry, and evaluation of reagent addition times. The scope of the reaction was evaluated by screening different types of 2-methylenetetrahydropyrans and electrophiles.

Scheme 2.1



2.2 Background and Significance

Exocyclic enol ethers have been scarcely used as nucleophiles in carbon-carbon bond-forming reactions, most likely due to the tendency of these systems to undergo isomerization and hydrolysis in the presence of trace acid or heat.¹ Nonetheless chemical transformations can be successfully applied to these moieties as previously discussed. Endocyclic enol ethers have been more extensively studied as nucleophiles in carbon-carbon bond forming processes. These aldol-like reactions typically involve the Lewis-acid catalyzed addition of an endocyclic enol ether to an acetal or aldehyde, followed by secondary nucleophilic attack of the resulting oxonium ion. Such processes have been studied by Mukiyama,² Sugimura,³ and Ghosh.⁴ Ghosh later applied three-component coupling strategies towards the synthesis of natural products and biologically active substrates.⁵

Mukiyama initially reported the use of endocyclic enol ethers as nucleophiles in carbon-carbon bond-forming transformations.² This methodology employed acetals as electrophiles, which were coupled to electron rich olefins under mild conditions. Olefin substrates included both endocyclic and vinyl ethers, as well as styrene. In most cases the best results were obtained using tin chloride and trimethylsilylchloride as an activator (Table 2.1, entries 1-4, and 6). Yields were optimized for the reaction between enol ether **315** and acetal **307** through use of a different activator, tin triflate and trityl chloride (entry 5). In the case of tetrahydropyran **306**, three adjacent stereocenters were created, giving rise to a complex mixture of diastereomeric products.

Styrene **317** provided a mixture of the desired aldol-like product along with chloride **318**. When conditions were modified such that one equivalent of trimethylsilylchloride was used, the corresponding chloride **318** was isolated in 80% yield as the sole product (Table 2.1, entry 6).

Table 2.1: Mukiyama Electrophilic Addition to Dihydropyrans

Entry	Olefin	Acetal	Activator	Product	Yield	dr
1			SnCl ₂ + TMSCl ^a		84	70:14:13:3
2			SnCl ₂ + TMSCl ^a		55	75:25
3			SnCl ₂ + TMSCl ^a		64 ^b	-
4			SnCl ₂ + TMSCl ^a		70 ^b	-
5			Sn(OTf) ₂ + TrCl ^a		74 ^c	60:40
6			SnCl ₂ + TMSCl ^d		80	55:45

^a1 eq of SnCl₂ used with 10 mol % TMSCl or TrCl

^bmixture of diastereomers

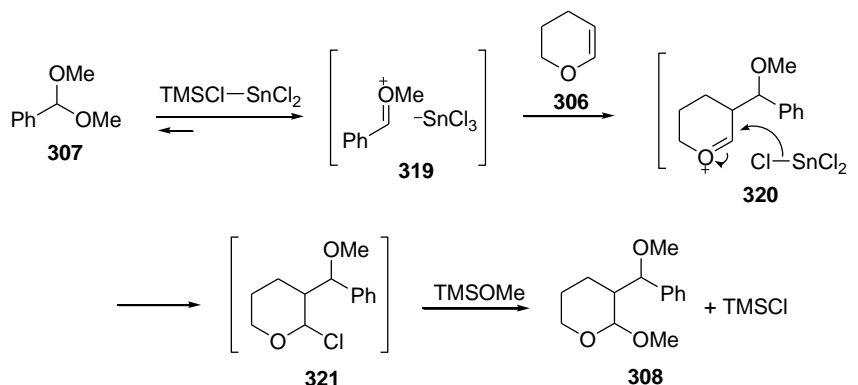
^cQuenched with NaOMe

^d1 eq of both SnCl₂ and TMSCl used

These results suggest the chloride as a key intermediate in the reaction path (Scheme 2.2). The first step in the reaction mechanism is the activation of acetal **307** by the tin catalyst, resulting in oxonium ion **319**. Generation of oxonium intermediate **319** is followed by nucleophilic addition

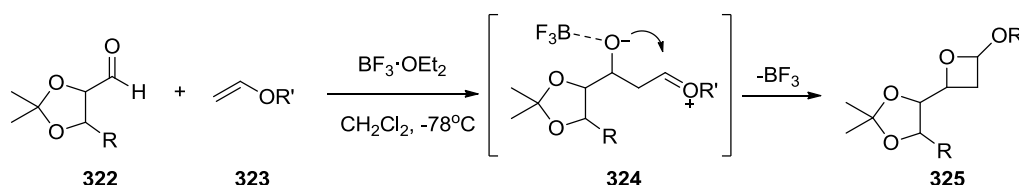
of dihydropyran **306**, and provides the intermediate chloride **321** after chlorine addition. Chloride **321** is in turn replaced by methoxide to provide tetrahydropyran **308**.

Scheme 2.2



A similar methodology was developed by Sugimura whereby enol ethers were combined with aldehydes to yield oxetane substrates.³ Lewis acid activation of aldose aldehyde derivatives **322** was followed by nucleophilic attack of enol ether **323**, resulting in zwitterion **324** (Scheme 2.3). Intramolecular addition of the oxide into the oxonium ion provided oxetane **325**.

Scheme 2.3



Reaction yields and the extent of Lewis acid loading varied based on substrate. The reaction proceeded in moderate to high yields with enol ethers **326** and **329** and aldehyde **327** (Table 2.2, entries 1 and 2). Use of both cis and trans enol ethers **329** and **331** resulted in similar yields of the same cis product **330** (entries 2 and 3). The reaction yield dropped dramatically with dihydropyran **306** acting as the olefin despite equimolar addition of Lewis acid (entry 4). Aldehydes **333** and **336** were examined for use in the

Table 2.2: Formation of Oxetanes from Enol Ethers

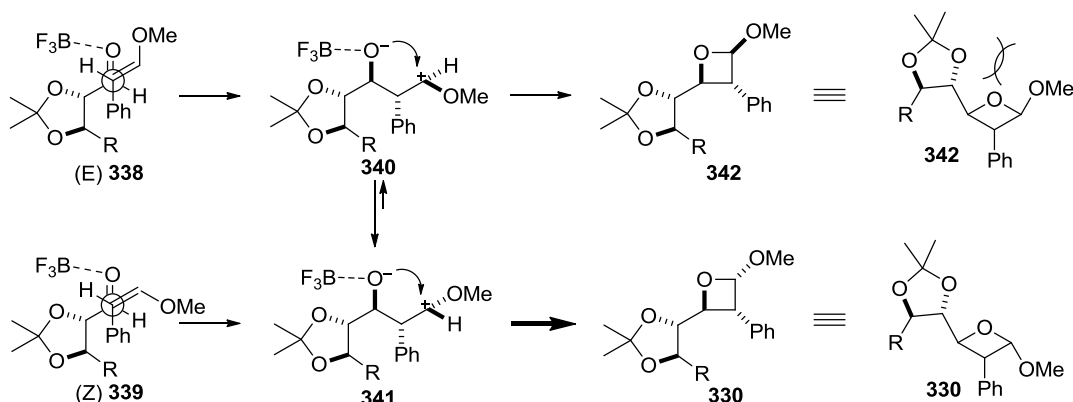
Entry	Olefin	Eneophile	BF ₃ -OEt ₂ (eq)	Product	Yield
1	H ₂ C=CHOEt 326		0.1		94%
2	PhHC=CHOMe 329		0.1		80%
3	PhHC=CHOMe 331		0.1		75%
4			1.0		39%
5	H ₂ C=CHOEt 326		0.05		64% + 27%
6	PhHC=CHOMe 329		0.1		21%

coupling reaction. Aldehyde **333** resulted in a diastereomeric mixture of products and aldehyde **336** produced desired cycloadduct **337** in low yield (entries 5 and 6).

The stereoselective outcome is consistent with Cram's cyclic chelation model where the nucleophile adds from the less hindered side. Additionally, the same oxetane product **330** was

formed with both the E and Z enol ethers **329** and **331**. Both E and Z enol ethers **329** and **331** result in similar reaction intermediates **340** and **341**. The reaction proceeds preferentially through intermediate **341** to produce the observed cis product **330**. Most likely the stereoselective outcome is based on reducing the steric and electronic repulsion between the methoxy group and the sugar side-chain (Scheme 2.4).

Scheme 2.4



In 1999, Ghosh reported a three-component coupling methodology towards the synthesis of 2,3-disubstituted tetrahydropyrans and tetrahydrofurans.^{4a} This reaction employed enol ethers and ethyl glyoxylate (**343**) in an efficient, high yielding, and one-pot aldol-type reaction. Titanium(IV) chloride activates glyoxylate **343**, leading to formation of oxonium species **344**, which can be trapped with secondary nucleophiles (Table 2.3). Ethyl glyoxylate was exclusively used as the electrophilic component in this reaction. These aldehydes possess high reactivity and form bidentate coordination complexes with Lewis acids.

The three-component coupling products were formed in good yield from vinyl enol ethers **345** (Table 2.3, entry 1), **347** (entry 2), and **306** (entries 3, 4, and 5). Allyltrimethylsilane (entries 1 and 4), triethyl silane (entries 2 and 3), and methanol (entry 5) all effectively trapped oxonium

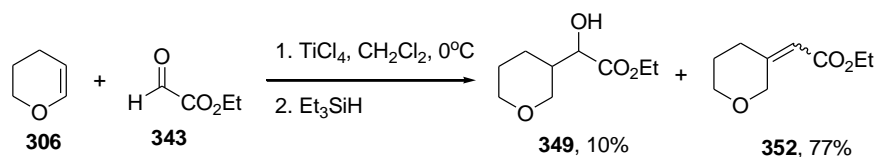
species **344** to yield coupled products **346** and **348-351**. These products were all formed in good yield with little to no diastereoselectivity.

Table 2.3: Three-Component Coupling of Enol Ethers with Ethyl Glyoxylate

Entry	Enol ether	Nucleophile	Product	Yield	dr
1	345	$\text{Me}_3\text{Si}-\text{CH}_2\text{CH}=\text{CH}_2$	346	83	1:1
2	347	Et_3SiH	348	88	1:1
3	306	Et_3SiH	349	95	1:1
4	306	$\text{Me}_3\text{Si}-\text{CH}_2\text{CH}=\text{CH}_2$	350	85	1:1
5	306	MeOH	351	65	2:1

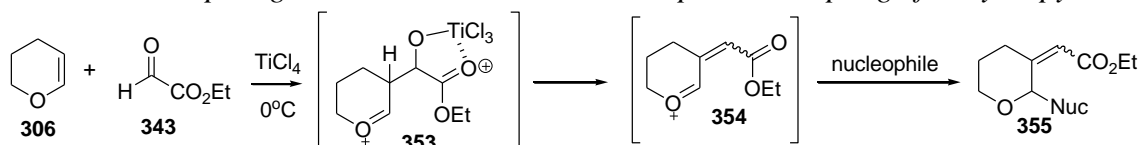
Modification of reaction conditions, whereby the reaction is run at 0°C, led to the isolation of elimination products **352** (Scheme 2.5).^{4a} Optimization of the reaction

Scheme 2.5



conditions resulted in exclusive formation of elimination products **352** (Table 2.4). This reaction provides an entry into the synthesis of functionalized 3-methylene tetrahydropyrans, a less common type of tetrahydropyranyl derivative. A number of different secondary nucleophiles were effective in trapping the tetrahydropyranyl alkenes including silanes (Table 2.4, entries

Table 2.4: Competing Elimination in the Three-Component Coupling of Dihydropyran



Entry	Nucleophile	Product	Yield	Ratio (E:Z) ^a
1	Et_3SiH		95	1:2
2	$\text{Me}_3\text{SiCH}_2\text{CH}=\text{CH}_2$		83	1:2
3	Me_3SiCN		84	7:1
4	MeOH		74 ^b	3:2
5	EtSH		46 ^b	3:2
6	PhSH		35 ^b	3:2

^aratio determined from ^1H NMR

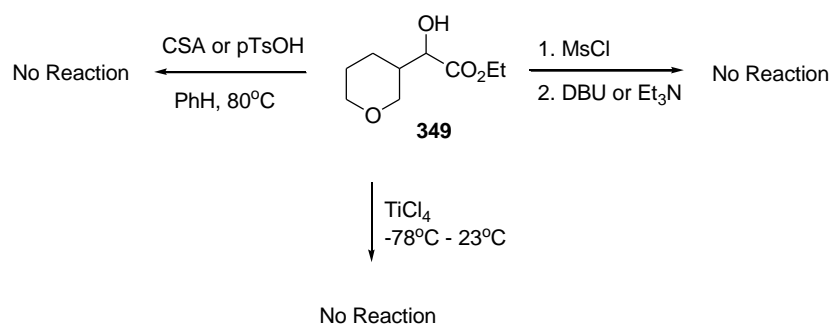
^bWith addition of 2 equiv of $i\text{Pr}_2\text{NEt}$

1, 2 and 3), methanol (entry 4), and thiols (entries 5 and 6). Yields for this process were good except for the use of thiols as secondary nucleophiles. Subjection of dihydrofurans to the same reaction conditions did not provide the elimination products solely, but produced poor reaction mixtures of the 3-methylenetetrahydrofurans and corresponding hydroxy three-component coupling products.

Interestingly, the corresponding hydroxy tetrahydropyranyl three-component coupling products are not prone to elimination. Both subjection of tetrahydropyran **349** to

camphorsulfonic acid and *p*-toluenesulfonic acid in refluxing benzene as well as the application of basic elimination conditions to the corresponding mesylate (DBU and triethylamine) did not yield eliminated product **352** (Scheme 2.6). The lack of elimination in the hydroxide product indicates that it is the oxonium ion-titanium complex **353** that is prone towards elimination. The same oxonium ion intermediate presumably forms, however elimination of the titanium as titanium dioxide yields α,β -unsaturated ester **352** after secondary nucleophile addition.


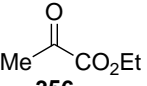
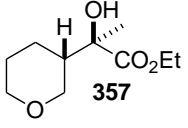

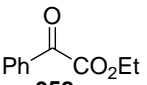
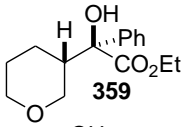

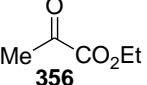
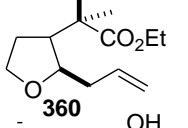
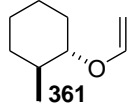
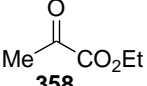
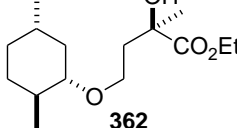
Scheme 2.6



When pyruvates were employed in place of glyoxylates the three-component coupling reaction occurred with good to excellent levels of diastereoselectivity (Table 2.5).^{4b} This process results in the stereoselective preparation of quaternary centers. Excellent diastereoselectivity resulted for the three component coupling reaction of dihydropyran **306** (entries 1 and 2) and dihydrofuran **347** (entry 3) using both methyl and phenyl pyruvates **356** and **358** with triethylsilane. A lower yield and diastereoselectivity was observed for chiral enol ether **361** (entry 4). Diastereomer ratios were determined by ¹HNMR and relative stereochemistry was determined by X-ray crystallography.

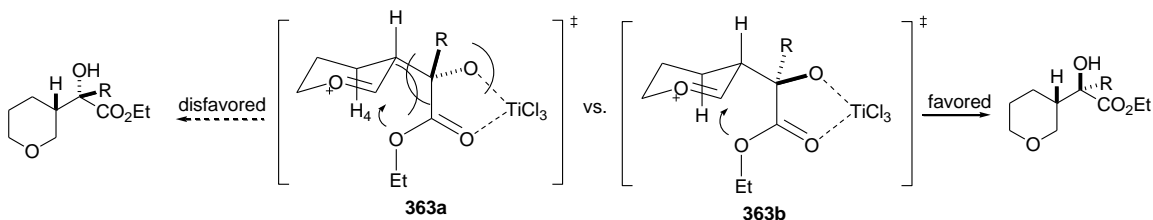
The observed diastereoselectivity can be explained by consideration of the following transition state (Scheme 2.7). The proposed transition state correctly predicts that the major diastereomer is formed preferentially. Both transition state **363a** and **363b** are stabilized by the

Table 2.5: Three-Component Coupling of Enol Ethers with Pyruvates

$\text{RO-CH=CH}_2 + \text{R-C(=O)CO}_2\text{Et} \xrightarrow[2. \text{ nucleophile}]{1. \text{ TiCl}_4, \text{ CH}_2\text{Cl}_2, 0^\circ\text{C}}$ $\text{RO-CH(R')-CH(OH)-CO}_2\text{Et}$						
Entry	Enol ether	Pyruvate	Nucleophile	Product	Yield	dr
1			Et ₃ SiH		82%	>99:1
2			Et ₃ SiH		77%	>99:1
3			Et ₃ SiH		83%	>99:1
4			Et ₃ SiH		65%	1:1

lone-pair donation of the ethoxy oxygen into the C₂ portion of the carbenium ion, yielding a ring-like transition state. Transition state **363a** experiences an unfavorable interaction between the H₄ axial hydrogen with the chelated titanium species. When the stereochemistry on the side chain is switched, as is the case for transition-state **363b**, the titanium species resides on the top-face where steric crowding is avoided.

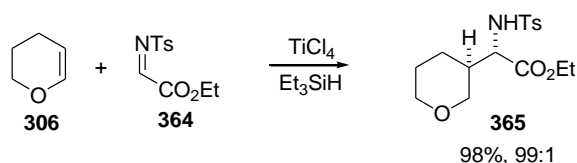
Scheme 2.7



Since the initial investigation of the three-component coupling methodology, this transformation has been applied to a number of systems including the synthesis of amine

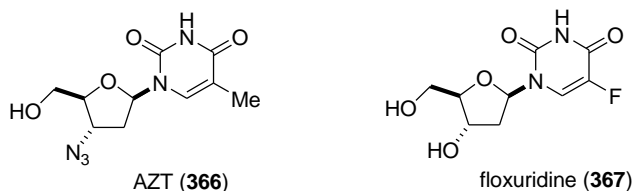
derivatives,^{5b} substituted pyrrolidines and prolines,^{5c} modified nucleosides,^{5e} cyclopentenoids,^{5d} and the natural product eburnamnine.^{5a} Aminotetrahydropyrans were created using *N*-tosyliminoesters as partners in the three-component coupling with dihydropyran **306** (Scheme 2.8).^{5b} *N*-tosyliminoesters **364** acted as good electrophilic components in this reaction and gave the corresponding tetrahydropyranyl products **365** in good to excellent yields. Diastereoselectivity varied with substrate and secondary nucleophile used.

Scheme 2.8



Ghosh later applied the three-component coupling methodology towards the manufacture of biologically significant substrates. The coupling of dihydrofurans, ethyl glyoxylate, and purine or pyrimidine bases resulted in formation of modified nucleosides with excellent diastereoselectivities. The synthesis of modified nucleosides is valuable because of their widespread applications as antiviral, antitumor, and antibacterial agents.⁶ Furthermore modified nucleosides have been used as treatments for AIDS, herpes, hepatitis, and cancer.⁷ In particular, AZT (**366**) and floxuridine (**367**) have been synthesized and used in treatments for HIV/AIDS and cancer respectively (Figure 2.1).

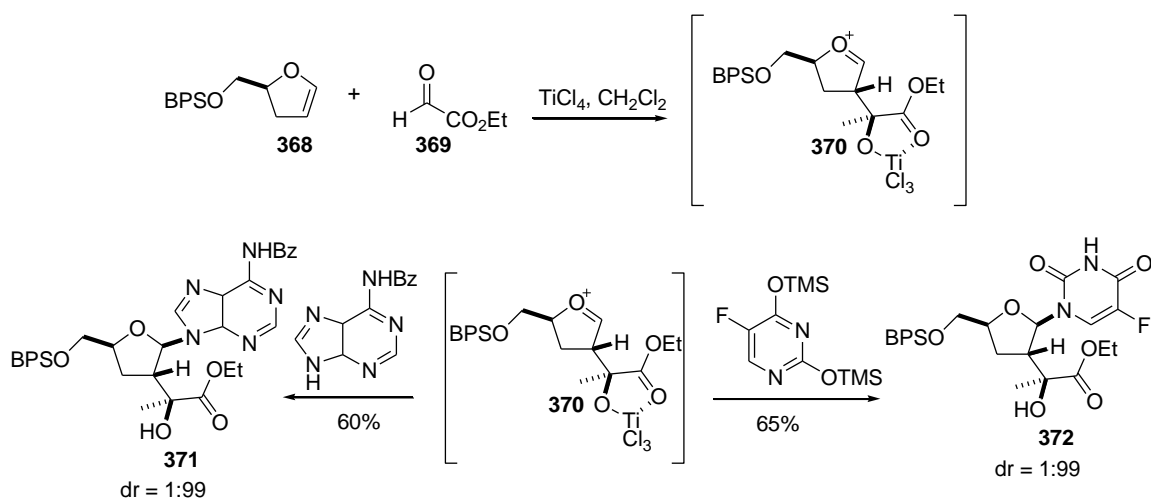
Figure 2.1



Ghosh utilized the three component coupling methodology designed in his lab to synthesize modified nucleosides (Scheme 2.9).^{5e} Lewis acid activation of ethyl pyruvate **369** and

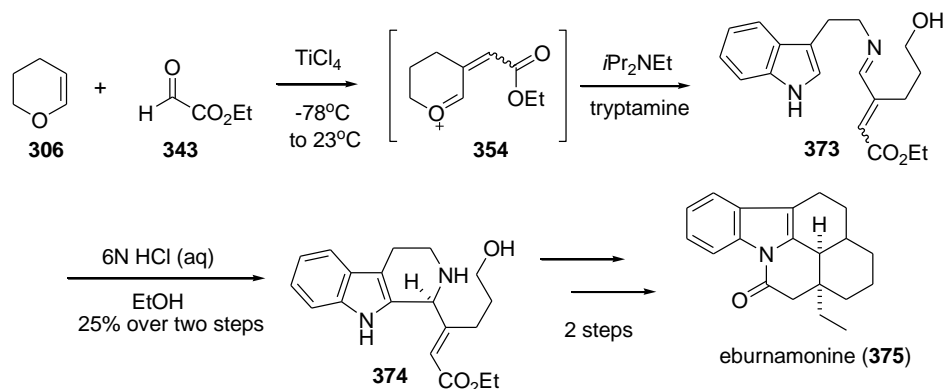
subsequent attack by dihydrofuran **268** yielded oxonium ion **370**. Subsequent attack of intermediate **370** with a purine or pyrimidine nucleophile furnished modified nucleosides **371** and **372**.

Scheme 2.9



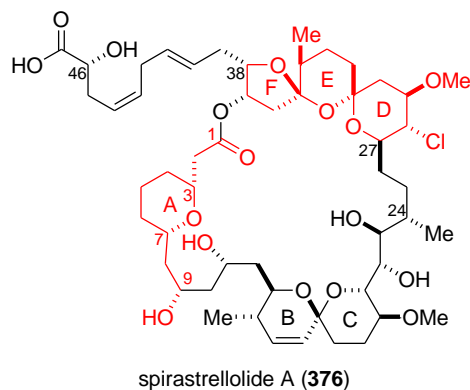
Ghosh extended the three-component coupling research to natural product synthesis. Eburnamonine (**375**) was synthesized in four steps from dihydropyran **306** (Scheme 2.10). Three component coupling of dihydropyran **306** with ethyl glyoxylate **343** and equimolar amounts of titanium(IV) chloride provided oxonium intermediate **354**. Secondary nucleophilic addition of tryptamine yielded imine **373** as a mixture of diastereomers (E:Z = 1.2:1). Because separation of the imines led to decomposition, subsequent cyclization was performed on the diastereomeric mixture in aqueous acid, providing amine **374** as the only diastereomer over two steps, albeit in low yield. Attempts at improving the 25% yield using different acids resulted in similar yields. Presumably cyclization only occurred on the E-isomer, while the Z-isomer decomposed under the reaction conditions. The natural product was obtained from intermediate **374** in two successive steps.

Scheme 2.10



The interest in natural product synthesis led our group towards the development of a mild reaction protocol between exocyclic enol ethers and electrophiles. Spirastrellolide A is a potent and selective inhibitor of Ser/Thr protein phosphatase 2A and thus a potential anticancer agent of synthetic interest (Figure 2.2).⁸ Initially, relative configurations were determined for three

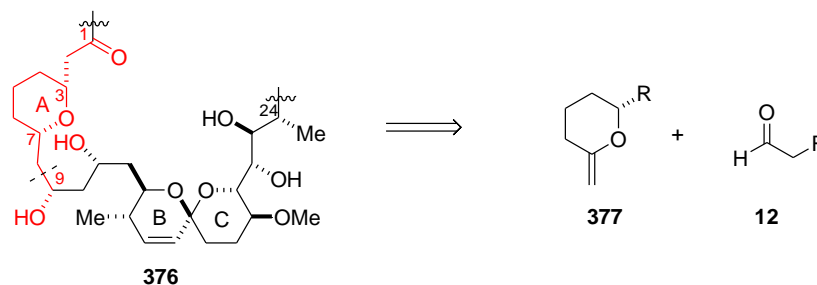
Figure 2.2



segments ($\text{C}_3\text{-C}_7$, $\text{C}_9\text{-C}_{24}$, and $\text{C}_{27}\text{-C}_{38}$), however, the stereochemical relationships between segments was not discovered until spirastrellolide B furnished structural insight.⁹ The lack of known relative stereochemistry led us to disconnect spirastrellolide at the $\text{C}_8\text{-C}_9$ bond (Scheme 2.11). The creation of the $\text{C}_8\text{-C}_9$ bond of spirastrellolide requires mild reaction conditions that do not result in β -elimination of the C_9 oxygen. Addition of a neutral nucleophile to an aldehyde

may be the best method for attaining the desired coupling, because anion addition to an aldehyde would undoubtedly yield elimination products. Therefore we sought to develop an aldol-like process with aldehydes using neutral exo enol ethers as nucleophilic substrates.

Scheme 2.11



As described, dihydropyrans and dihydrofurans are known to act as neutral nucleophiles in carbon-carbon bond-forming reactions with acetals or aldehydes. Similar application of exocyclic substrates to these aldol-like reactions has not been studied. The advantage of using 2-methylenetetrahydropyrans over endocyclic systems is that these groups possess higher levels of steric strain¹⁰ and a lower degree of stereoelectronic stability,^{11,12} resulting in a more highly activated nucleophile, although they are consequently prone to olefin isomerization. Our aim was to develop a coupling methodology between exo enol ethers and electrophiles such that addition will occur faster than double bond isomerization. The goal is to develop a general process that can be applied to a wide range of substrates using mild reaction conditions, all while yielding synthetically valuable tetrahydropyranyl ketides as products.

2.3 Results and Discussion

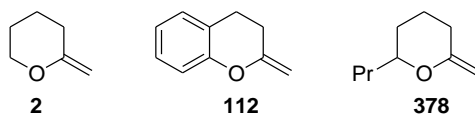
Because tetrahydropyranyl ketide moieties are present in bioactive natural products, new methods toward the synthesis of their analogs are synthetically significant. Our synthetic efforts toward β -hydroxy tetrahydropyrans include the use of exo enol ethers as neutral nucleophiles in a three component coupling reaction. The three-component coupling of 2-

methylenetetrahydropyrans was developed through synthesis of the exocyclic enol ether components, and then subjection of these substrates to various Lewis acid conditions in conjunction with electrophilic components and secondary nucleophiles. After optimization of reaction conditions, the substrate scope of the reaction was evaluated through evaluation of different exo enol ethers and electrophiles.

Synthesis of Exocyclic Enol Ethers

Earlier reports have suggested the feasibility of exo enol ethers acting as nucleophiles in three-component coupling.^{13,14} Appropriate exo enol ethers were prepared to explore their possible use in three component coupling with electrophiles. Exo enol ethers **2**, **112**, and **378** were synthesized (Figure 2.3). Exo enol ether **2** was used to screen suitable reaction conditions. The other enol ethers allowed us to evaluate scope of the reaction, including the use of less electron rich enol ethers (**112**).

Figure 2.3

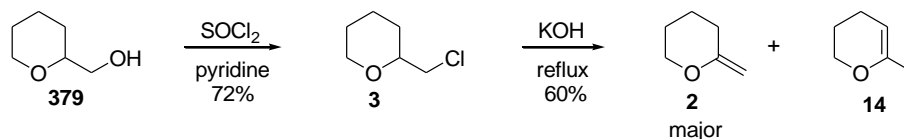


Preparation of enol ether **378** provided an opportunity to evaluate how a preexisting stereocenter affects the diastereoselectivity of the three component coupling reaction. Enol ether **2** is synthesized through dehydrohalogenation whereas enol ethers **112** and **378** are prepared from corresponding lactones using Petasis olefination.¹⁵ The synthesis of these enol ethers is discussed herein.

2-Methylenetetrahydropyran **2** was prepared from 2-(hydroxymethyl) tetrahydropyran **379** using a two-step literature procedure (Scheme 2.12).^{16,17,18} Alcohol **379** was converted to the corresponding alkyl chloride **3** upon treatment with thionyl chloride. Subsequent elimination

was achieved upon heating halide **3** in the presence of powdered KOH. Resulting enol ethers **2** and **14** were isolated by distillation from the reaction mixture as, at best, a 38:1 ratio, with the exocyclic isomer predominating.

Scheme 2.12



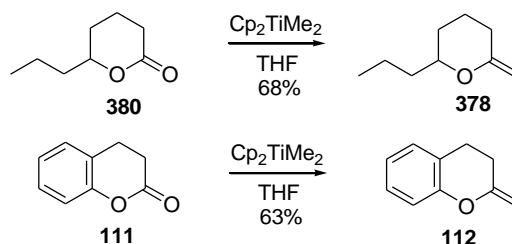
Dehydrohalogenation proved to be a successful method toward synthesis of enol ether **2**. The volatility of this enol ether makes its preparation from δ -valerolactone difficult using Petasis's olefination methodology. However, dehydrohalogenation is problematic in that a mixture of isomers results in the distilled product. The ratio of exo to endo enol ethers deviated considerably, from 3:1 to 38:1 with no discernable reason for the variation. Unwanted isomerization could be somewhat minimized through use of base-washed glassware. The minimum ratio of exo to endo cyclic enol ether used for the three-component coupling project was 10:1. Although a minimal amount of endocyclic enol ether is present in the three-component reaction mixture, and endocyclic enol ethers have been shown to participate in three component coupling reactions,^{4a} it is believed to have little effect on the reaction. The exo enol ethers should be much more reactive towards the three component coupling reaction because of their high steric strain¹⁰ and low stereoelectronic stability.^{11,12}

Preparation of the exo enol ether was further complicated by its co-distillation with water. The presence of water is problematic in the subsequent three-component coupling reaction because isomerization of the exocyclic enol ether to the endo enol ether proceeds with the production of protic acid from Lewis acid and water. Hydrolysis of the resulting three-component coupled product is also possible. A number of desiccants were used to eliminate the

excess water from the distilled product, KOH, CaH, P₂O₅, and K₂CO₃, however addition of solid sodium metal yielded the best results.

Enol ethers **378** and **112** were both synthesized from commercially available octanolactone **380** and dihydrocoumarin **111** respectively through direct olefination (Scheme 2.13).¹⁹ The synthesis of enol ether **378** was achieved upon treatment of octanolactone **380** with

Scheme 2.13



freshly prepared dimethyl titanocene (Petasis reagent) in refluxing THF. Purification of the enol ether was achieved through trituration with hexanes and subsequent flash column chromatography using a 5% solution of Et₃N in hexanes. Addition of Et₃N to the column is essential to avoid isomerization of the exo enol ether on the acidic silica. By this method, enol ether **378** was isolated in 68% yield as a single regioisomer. Enol ether **112** was prepared similarly from dihydrocoumarin **111**. Exo enol ether **112** was isolated in good yield as a single regioisomer. Without the need for a water work-up, Petasis olefination repeatedly provided exo enol ethers without competing endocyclic enol ether formation. With the exo enol ethers in hand, we next evaluated their utility as nucleophiles in the three-component coupling reaction.

Three-Component Coupling of 2-Methylenetetrahydropyrans

To demonstrate the feasibility of the three component coupling reaction of exo enol ethers, we first looked at the reaction of 2-methylenetetrahydropyran with ethyl glyoxylate and triethylsilane (Table 2.6). Preliminary studies included screening Lewis acids and identifying suitable reaction conditions to effect the transformation and optimize yield.²⁰

Initial efforts focused on screening Lewis acids (Table 2.6). The reaction was carried out by combining equal amounts of the enol ether and electrophile in dichloromethane at -78°C . Addition of Lewis acid immediately followed. After the reaction had stirred for an hour, three equivalents of triethylsilane were added and the reaction was left to stir at -78°C for an additional five hours. Work up conditions included addition of aqueous sodium bicarbonate at -78°C , isolation of the organic layer, and flash column chromatography.²¹

Table 2.6: Initial Conditions for Three-Component Coupling of Exo Enol Ethers

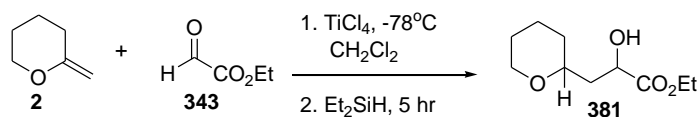
Entry	Lewis acid	Yield (%)
1	SnCl_4	0
2	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	0
3	ZnCl_2	0
4	EtAlCl_2	0
5	Et_2AlCl	0
6	TiCl_4	48

Prior work by Mukaiyama² and Ghosh^{4a} suggests the need for a strong Lewis acid to effect an aldol-like addition of enol ethers to electrophiles. Therefore we began our study by looking at relatively strong Lewis acids. Use of tin chloride (entry 1, Table 2.6) did not produce the desired tetrahydropyranyl product, although this Lewis acid was successfully used in Mukaiyama's transformations. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (entry 2) was also unsuccessful in generating the reaction. Zinc chloride (entry 3), a weaker Lewis acid, was also evaluated. Rather than producing the desired tetrahydropyranyl product, a dihydropyranyl ene adduct was formed. Ethyl aluminum dichloride and diethyl aluminum chloride (entries 4 and 5) both did not yield the desired product.²¹

Finally, titanium(IV) chloride was examined. This Lewis acid was previously reported by Ghosh to transform dihydropyrans to three component coupled products. Alas titanium(IV) chloride produced our coupled product **381**, albeit in modest yield, and this success encouraged us to continue our studies. This data demonstrated the feasibility of the three component coupling reaction of exocyclic enol ethers with ethyl glyoxylate and the use of exo enol ethers as neutral nucleophiles.

In an effort to optimize yield, the time between the addition of titanium(IV) chloride to the reaction mixture and addition of the secondary nucleophile, triethylsilane, was evaluated (Table 2.7). Initial reaction conditions involved stirring enol ether **2** with Lewis acid an hour prior to triethylsilane addition (entry 1, Table 2.7). There was effectively no change in reaction yield when the stirring time between the enol ether and Titanium(IV) chloride was reduced to twenty minutes (entry 2). A modest increase in

Table 2.7: Evaluation of Reaction Time in The Three-Component Coupling Reaction



Entry	Time ^a	Yield (%)
1	1 hr	48
2	20 min	45
3	10 min	59
4	0 min	86

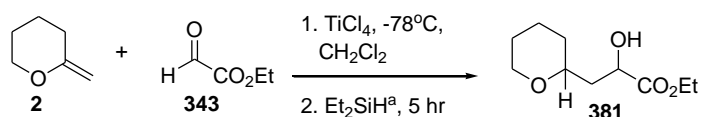
^aTime reaction stirred before triethylsilane addition
1:1 mixture of **2** and **343**

yield was observed when the time was further reduced to 10 minutes (entry 3). The best results were obtained when triethylsilane was added to the enol ether prior to the Lewis acid (entry 4). The best yields were obtained with instant access to the reducing agent, indicating that

immediate reduction of the oxonium ion intermediate was key in production of the coupled product. Instant reduction of the oxonium intermediate following its formation could prevent the decomposition of this reaction intermediate and the production of other side-products.²¹

Finally, changes to the reaction stoichiometry were evaluated, whereby the relative amounts of enol ether, electrophile, and Lewis acid were varied. The ratio of exocyclic enol ether to ethyl glyoxylate was determined to be of little consequence to the reaction yield. Use of either reactant in modest excess gave comparable yields of the tetrahydropyranyl ketide **381** (entries 1 and 2, Table 2.8). Again, the best yields for the three-component coupling reaction

Table 2.8: Study of Reaction Equivalents in Three-Component Coupling Reaction



Entry	Ratio 1:18	Lewis Acid eq.	Time ^b	Yield (%)
1	1:1.2	1	1 hr	48
2	1.5:1	1	1 hr	56
3	1:1.2	1	0 min	86
4	1:1.2	1	0 min	86
5	1.2:1	1	0 min	84
6	1:1.2	0.5	0 min	45
7	1:1.2	0.2	0 min	23
8	1:1.2	0.1	0 min	10

^aThree equivalents used except entry **4** where amount of triethylsilane was reduced to 1 equivalent

^bTime reaction stirred before addition of triethylsilane

were observed when the triethylsilane was added prior to Lewis acid addition, however the ratio of enol ether to aldehyde still had little consequence on the reaction yield (entries 3 and 5). Nonetheless ethyl glyoxylate was used in slight excess for the remainder of the experiments

because it was more difficult to accurately determine the exact amount utilized in the reaction due to its tendency towards polymerization.²¹

Both excess and equimolar amounts of triethylsilane were equally effective in the three component coupling transformation (entries 3 and 4). Therefore only one equivalent of triethylsilane was used in the reactions that followed these experiments. Reducing the amount of triethylsilane in the reaction mixture not only increases the reaction economy, but also reduces any unwanted reduction in the products.²¹

Of greater significance was the quantity of titanium(IV) chloride used. The best yields for the three-component coupling reaction were obtained using equimolar amounts of the Lewis acid (entry 3, Table 2.7). When the amount of titanium(IV) chloride was reduced, there was a proportional decrease in the reaction yield. An 84% yield was achieved with a full equivalent of Lewis acid (entry 3). The yield was nearly cut in half (45%) with use of half an equivalent of Lewis acid (entry 5), and likewise yields of 23% and 10% were observed when the Lewis acid was reduced to 20 and 10 mole percent respectively (entries 6 and 7).²¹

The preliminary experiments demonstrated the feasibility of the three component reaction of exo enol ethers with ethyl glyoxylate. The best results were obtained using equimolar amounts of the aldehyde in the presence of a full equivalent of titanium(IV) chloride when time between oxonium ion intermediate formation and addition of the secondary nucleophile is minimized.

Once the basic reaction was demonstrated, studies were expanded to evaluate the scope and stereoselectivity of the three component coupling reaction (Table 2.9). Of particular interest was the range of electrophiles that could be used for this transformation. For these studies both triethylsilane and allyltrimethylsilane were used effectively at secondary nucleophiles. First

Table 2.9: Three-Component Coupling of Enol Ether **2** with Various Electrophiles

Entry	Enol Ether	Electrophile	Time ^a	Nucleophile	Product	Nu	Yield
1			5 min	Et ₃ SiH		381^d H	86%
2			5 min	CH ₂ =CHCH ₂ TMS		387^e CH ₂ =CHCH ₂	55%
3			1 hour	Et ₃ SiH		388^f H	79%
4			1 hour	CH ₂ =CHCH ₂ TMS		389^g CH ₂ =CHCH ₂	51% ^b
5			1 hour	Et ₃ SiH		390 H	trace ^c
6			1 hour	CH ₂ =CHCH ₂ TMS		391^h CH ₂ =CHCH ₂	38% ^b
7			1 hour	Et ₃ SiH		392 H	0% ^b
8			1 hour	Et ₃ SiH		393 H	0% ^b
9			1 hour	Et ₃ SiH		394 H	0% ^b

^aTime before nucleophile addition; ^bReaction performed by Dr. G. Liang; ^cBipproduct **396** primarily formed in % yield

^ddr 1:1 ; ^edr 1:2 ; ^fdr 1:4 ; ^gdr 1:2 ; ^hdr 1:3

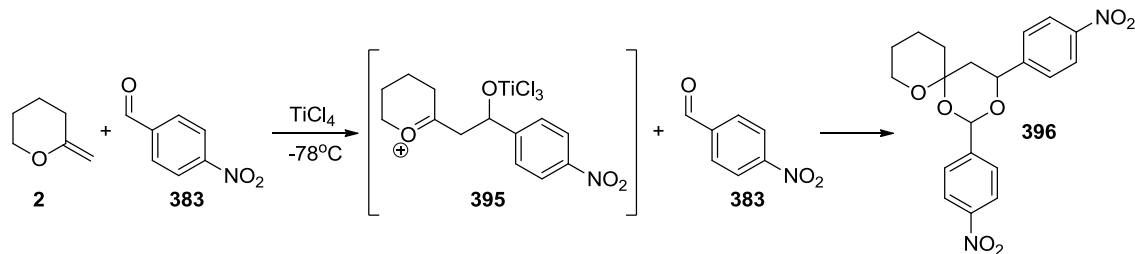
explored was the range of electrophiles that could be used for this transformation. Electron deficient aldehydes and ketones worked well in this reaction whereas simple aromatic and aliphatic aldehydes were unreactive under the reaction conditions. Excellent results were obtained with ethyl glyoxylate **343** and 2,3-butanedione **382**, using trimethylsilane as the secondary nucleophile (entries 1 and 3, Table 2.9). Product yields were slightly lower using

allyltrimethylsilane as the secondary nucleophile, but nonetheless resulted in synthetically useful quantities of the desired products (entries 2 and 4). The reaction was found to be efficient when triethylsilane and allyltrimethylsilane were both added to the reaction mixtures five minutes after the other components. A slight delay in reducing agent addition provided quick access of the secondary nucleophile to the oxonium ion intermediate, while avoiding direct reduction of the aldehyde.

The examples utilizing a ketone as the electrophile (entries 3 and 4, Table 2.9) are intriguing because an oxygen-containing quaternary center is formed. If allyltrimethylsilane is used as the secondary nucleophile two adjacent quaternary centers are formed. Secondly the aldol-like transformation with 2,3-butanedione proceeds fairly rapidly in good to excellent yield whereas most reversible aldol transformations involving ketones favor the reverse reaction and fail to produce products in appreciable yields.

The reaction of enol ether **2** with *p*-nitrobenzaldehyde **383** was less successful and resulted in production of byproduct **396** along with low yields of the three-component coupled products **390** and **391** (entries 5 and 6, Table 2.9). Upon formation of oxonium ion intermediate **395**, a competing reaction transpires with unreacted *p*-nitrobenzaldehyde **383** to give spiroketal product **396** (Scheme 2.14). No reaction was observed using unactivated aliphatic and aromatic aldehydes such as octyl aldehyde **384** (entry 7), benzaldehyde **386** (entry 8), and trifluoroacetone **387** (entry 9).

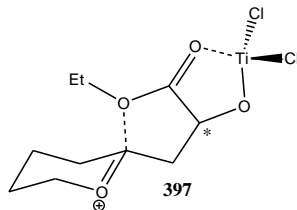
Scheme 2.14



The three component coupled products were isolated as mixtures of diastereomers because they were inseparable by chromatographic methods. Diastereomer ratios were determined from ^1H NMR integrations of purified products, however the relative stereochemistry of the products was not determined. Generally, little diastereoselectivity was observed for this process, resulting in stereoisomers that were isolated in ratios of 1-3:1 with the exception of tetrahydropyran **388**. Tetrahydropyran **388** was produced as a 4:1 ratio of diastereomers.

The initial addition of the enol ether to the electrophile almost certainly proceeds unselectively. The addition of the secondary nucleophile to the oxonium intermediate is what gives rise to the observed diastereomeric ratios. The oxonium ion intermediate formed is likely stabilized through addition of a lone pair from an ethoxy or carbonyl oxygen into the pseudo-axial vacant orbital (Figure 2.4). Based on this conformation, the direction of secondary nucleophile addition into the oxo carbenium ion most likely occurs from the non-hindered bottom face, although a higher energy, boat-like transition state is required. Note that a simple chair flip would give rise to the opposite stereoisomer in equal amounts. Thus a 1:1 ratio of diastereomers is expected and addition from either face does not preferentially correlate with the initial hydroxy stereocenter formed.

Figure 2.4



Although a 1:1 mixture of diastereomers is predicted, higher ratios are experimentally obtained. Most noteworthy is the addition of 2-methylenetetrahydropyran to 2,3-butanedione, which yields a 1:4 diastereomeric ratio. There is no discernable reason that ketones should produce higher isomer ratios. Application of 2,3-butanedione to Figure 2.4 does not increase the facial preference towards secondary nucleophile addition. It must be noted that diastereomer ratios were obtained through ^1H NMR integrations for products purified by flash column chromatography. Although diastereomer ratios are typically measured from crude spectra, impurities present in the product mixtures made these measurements difficult. Even though a majority of the column fractions were collected, combined, and tested for diastereomer ratios, the ratios could be affected from this purification process.

Previous studies (Table 2.7) suggested the need to minimize the time between oxonium ion formation and addition of the secondary nucleophile. In practice, however, the optimum time before addition of the secondary nucleophile (“pre-stir” time) had to be carefully balanced against the reactivity of the electrophile to avoid direct addition of triethylsilane to the carbonyl instead of the oxonium ion intermediate. The reaction pre-stir times varied based on the degree of electrophile activation. As activation increased, oxonium ion formation proceeded more quickly. Therefore secondary nucleophiles were introduced to the reaction mixture sooner when more highly activated electrophiles were used. In the case of ethyl glyoxylate **343**, a pre-stir

time of only five minutes was required (entries 1,2, Table 2.9). With less activated enophiles pre-stir times of one hour were required (entries 3-6).

After study of 2-methylenetetrahydropyran in the three component reaction, we sought to extend the scope of enol ether used by evaluating dihydrocoumarin-derived enol ether **112** (Table 2.10). Enol ether **112** was expected to be less reactive than 2-methylenetetrahydropyran since the lone pair on oxygen is tied up in resonance with the aromatic ring. Nonetheless, the desired three component coupling resulted with excellent yields in the presence of electron deficient electrophiles and both triethylsilane and allyltrimethylsilane as secondary nucleophiles.

Table 2.10: Three-Component Coupling of Enol Ether **112** with Various Electrophiles

Entry	Enol Ether	Electrophile	Time ^a	Nucleophile	Product	Nu	Yield
1			5 min	Et ₃ SiH		398^c H	97% ^b
2			5 min	CH ₂ =CHCH ₂ TMS		399^d CH ₂ =CHCH ₂	97% ^b
3			1 hour	Et ₃ SiH		400^e H	87%
4			1 hour	CH ₂ =CHCH ₂ TMS		401^f CH ₂ =CHCH ₂	97% ^b
5			1 hour	Et ₃ SiH		402^g H	95%
6			1 hour	CH ₂ =CHCH ₂ TMS		403^h CH ₂ =CHCH ₂	97%

^aTime before nucleophile addition; ^bReaction performed by Dr. G. Liang; ^cdr 1:1; ^ddr 1:1; ^edr 1:5; ^fdr 1:1; ^gdr 1:2; ^hdr 1:1

Reaction of enol ether **112** with ethyl glyoxylate provided high yields of tetrahydropyran products with both triethylsilane and allyltrimethylsilane as secondary nucleophiles (entries 1 and 2, Table 2.10). Similar to the reaction of ethyl glyoxylate with enol ether **2**, the high

reactivity of ethyl glyoxylate necessitated only five minutes of pre-stir time between enol ether **112**, aldehyde, and Lewis acid before secondary nucleophile addition. Although less activated than ethyl glyoxylate, 2,3-Butanedione **382** (entries 3 and 4) and *p*-nitrobenzaldehyde **383** (entries 5 and 6) were successfully coupled with enol ether **112** in excellent yields.

The high yields observed for enol ether **112** are most likely attributed to the greater stability of this enol ether as compared to 2-methylenetetrahydropyran. The olefin owes its stability to the resonance it experiences with the aromatic ring. By having a greater level of stability, enol ether **112** is less likely to isomerize or decompose in solution. Secondly, enol ether **112** successfully produced product **402**, whereas addition of enol ether **2** to the same aldehyde, *p*-nitrobenzaldehyde **383**, failed as previously discussed (Scheme 2.9). The increased steric bulk enol ether **112** experiences is enough to hinder approach of a second *p*-nitrobenzaldehyde molecule towards the oxonium ion intermediate. Therefore product **402** could be isolated in 95% yield.

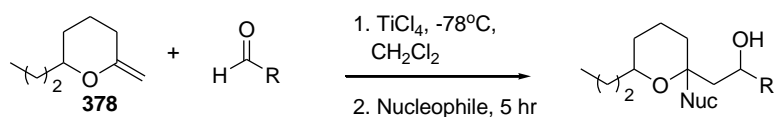
Like the 2-methylenetetrahydropyran examples (Table 2.9), the three component coupled products of enol ether **112** were isolated as mixtures of diastereomers. Diastereomer ratios were determined from the ¹H NMR integrations of purified products, and the relative stereochemistry was not determined. Here too the reaction generally proceeded with little diastereoselectivity except for the reaction with 2,3-butanedione and triethylsilane (entry 3).

The study of 6-propyl-2-methylenetetrahydropyran **378** provides an opportunity to explore the diastereoselectivity of the reaction when the enol ether bears a substituent at C₆. This system is similar to how the A-ring of spirastrellolide would be approached using this methodology. The reaction of 2-methylenetetrahydropyran **378** with ethyl glyoxylate provided desired β-hydroxytetrahydropyrans **404** and **405** in good to excellent yields with both

triethylsilane and allyltrimethylsilane as secondary nucleophiles (entries 1 and 2, Table 2.11) Use of 2,3-butanedione **382** as the electrophilic component also provided the desired coupled product in moderate yield (entry 3).

The three component coupled products of enol ether **378** have three stereocenters and thus four diastereomer products could result. Figure 2.5 indicates the two different types of relationships that exist between the stereocenters. If the C₂' hydroxy substituent and secondary nucleophile are on the same or opposite faces of the molecule they are said to be either syn or anti respectively. The other stereochemical relationship relates to the C₂ and C₆ ring substituents

Table 2.11: Three-Component Coupling of Enol Ether **378** with Various Electrophiles

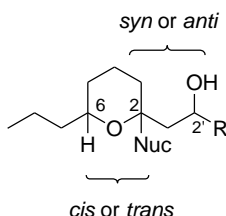


Entry	Enol Ether	Electrophile	Time ^a	Nucleophile	Product	Nu	Yield
1			5 min	Et ₃ SiH		404^b H	77%
2			5 min	CH ₂ =CHCH ₂ TMS		405^c CH ₂ =CHCH ₂	67%
3			1 hour	Et ₃ SiH		406^d H	56%

^aTime before nucleophile addition; ^bdr 1:5; ^cdr 1:1; ^ddr 1:2

These substituents are either cis or trans. Therefore the following four diastereomers could result: *cis, syn*; *cis, anti*; *trans, syn*; *trans, anti*.

Figure 2.5



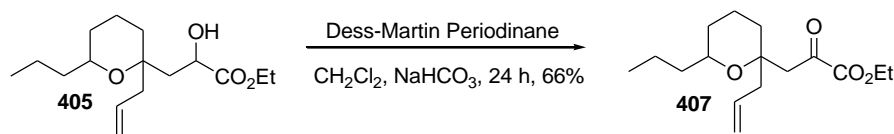
Results from the three component coupling of enol ether **378** indicated that only two diastereomers were formed. The diastereomeric ratios of tetrahydropyranyl products obtained are most likely derived from syn/anti relationships, because as previously discussed with the three component couplings of 2-methylenetetrahydropyrans, little to no stereoselectivity is expected at the newly generated C₂' stereocenter. Secondary nucleophile addition, however, is highly controlled by the pre-existing C₆ stereocenter on the enol ether. Nuclear Overhauser effect (nOe) studies of the resulting products confirmed this hypothesis by detecting only *cis*-configured products. Therefore only *cis*, *syn* and *cis*, *anti* products were obtained.

A 1:1 ratio of diastereomers results from the three component coupling of enol ether **378** to 2,3-butanedione (entry 2, Table 2.11), demonstrating the lack of stereoselective addition to the electrophile. The diastereomeric ratios of products **404** and **406** were 1:5 and 1:2 respectively (entries 1 and 3). Unlike previous examples where enol ethers **2** and **112** showed increased diastereomeric ratios for the 2,3-butanedione products, (entry 3, Table 2.9 and entry 3, Table 2.10), these results show an enhanced ratio for ethyl glyoxylate product **404** (entry 1). Again there exists no stereochemical model that would explain such a significant deviation from the expected 1:1 ratio of diastereomers. As previously discussed, purification of the crude product mixtures was necessary to determine diastereomer ratios. The diastereomer ratios could have been altered as a result of purification process.

All three component coupled products of enol ether **378** yielded only *cis*-2,6-substituted products, as was determined through nOe studies. In all cases the *trans* diastereomer was not observed. Oxidation of alcohol **405** was performed to simplify the ¹H NMR spectrum for nOe analysis (Scheme 2.15). Alcohol oxidation reduced the number of diastereomers from two to

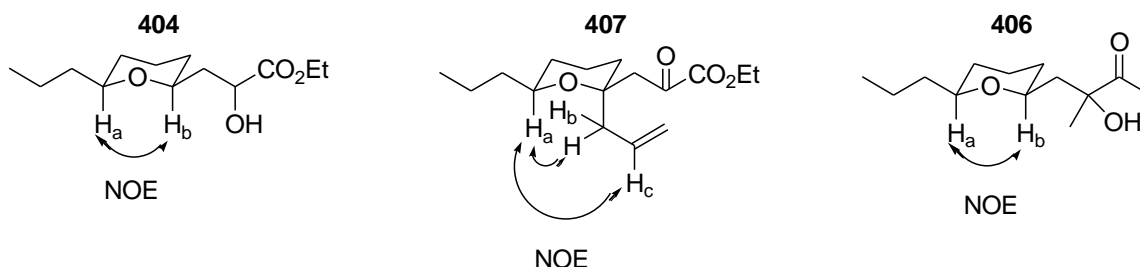
one, proving that the observed diastereoselectivity stems from the syn/anti selectivity, while also eliminating overlapping proton NMR signals.

Scheme 2.15



The individual resonances for the protons adjacent to the tetrahydropyranyl oxygen on product **404** were identified in the ^1H NMR on the basis of chemical shift. These two protons are also differentiated from the ethoxy protons, which integrate for two and have a quartet multiplicity. The relative stereochemistry at C_2 and C_6 was established by nOe experiments (Figure 2.6). Irradiation of H_a resulted in the enhancement of resonances due to H_b . A nOe was

Figure 2.6



not observed between either H_a or H_b and the C_2 or C_6 side chains. The nOe between H_a and H_b of alcohol **404** is only expected when the protons are on the same face of the tetrahydropyranyl ring.

Study of ketone **407** through nOe experiments also proved the preferential formation of 2,6-cis-products from the three component coupling of enol ether **378**. The proton resonance for H_a was determined by chemical shift, multiplicity, and integration. H_a was differentiated from the ethoxy protons, which integrate for two and display a quartet splitting pattern. The allyl proton resonances in the ^1H NMR spectrum derived from H_b were identified by chemical shift,

and were the only signals present in the 2.10-2.80 ppm range. The resonances due to H_c were identified by chemical shift and integration. Irradiation of H_a on tetrahydropyran **407** caused a strong enhancement in the resonances associated with H_b and H_c, but not with any signals associated with the C₂ sidechain. The nOe between H_a, H_b, and H_c of product **407** is expected only when the ring junction proton and allyl sidechain are on the same face of the tetrahydropyranyl ring.

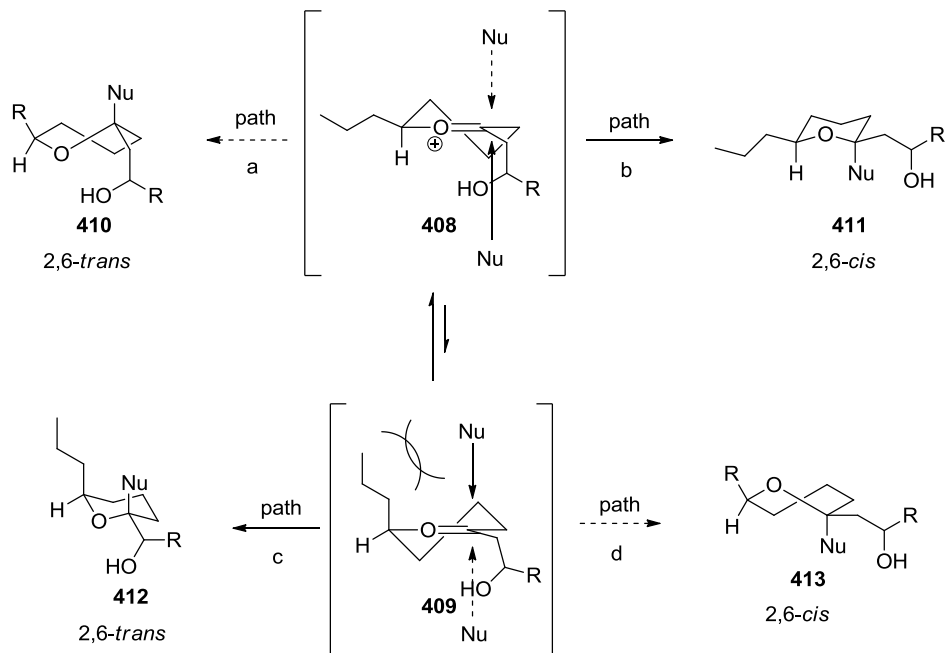
The relative stereochemistry about the tetrahydropyranyl ring of alcohol product **406** was determined similarly through nOe experiments, by separately irradiating both C₂ and C₆ protons. Both resonances associated with H_a and H_b were determined by chemical shift, and are the only two in the 3.10-3.50 ppm range. Upon irradiation of H_a, which resulted in the enhancement of resonances due to H_b. Likewise, irradiation of H_b caused enhancement in resonances due to H_a. A nOe was not observed between either irradiated protons and the C₂ or C₆ side chains. The nOe between H_a and H_b is only expected when these protons are on the same face of the tetrahydropyranyl ring. The three nOe experiments of products **404**, **407**, and **406** indicate that secondary nucleophile addition to the C₂ tetrahydropyranyl carbon is *trans* selective relative to the C₆ side chain. The 2,6-*cis* products result without detection of the 2,6-*trans* products.

The observed preference for formation of 2,6-*cis*-tetrahydropyranyl derivatives stems from both steric and stereoelectronic factors.²² The initial, nucleophilic attack by enol ether **378** results in formation of the oxonium ion intermediate. Subsequent attack of the oxonium ion intermediate by the secondary nucleophile is anticipated through one of two half-chair conformations (**408** and **409**, Scheme 2.16). Attack of these half-chairs from the top or bottom face through pathways a-d provides tetrahydropyrans **410-413**.

Half-chair conformers **408** and **409** exist in equilibrium, favoring half-chair **408**, which orients the propyl side chain pseudo equatorially. Addition of the secondary nucleophile through both pathways a and d (Scheme 2.16) is disfavored based on stereoelectronic grounds. The transition state for equatorial attack by the nucleophile requires a higher activation energy than the transition state for axial attack. The increased activation energy is derived from the high-energy, boat-like transition state.

Both pathways b and c proceed through more favorable, lower energy chair-like transition states. Of these pathways, c is disfavored on steric grounds. This transition state, which orients the n-propyl group pseudo axially, develops a severe 1,3-diaxial interaction

Scheme 2.16

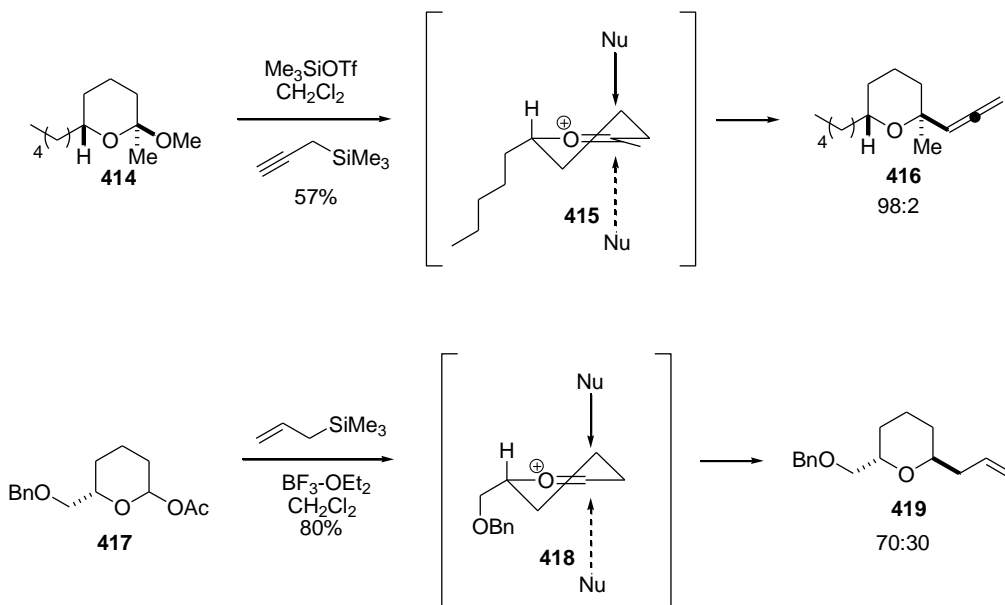


between the C₆ substituent and the incoming nucleophile. Therefore b is the kinetically favored pathway by which the selective secondary nucleophilic addition occurs. The secondary nucleophile preferentially adds *trans* to the C₆ substituent, resulting in 2,6-*cis*-tetrahydropyran product formation in reference to the propyl and β-hydroxy side chains. These are also the

thermodynamically favored products where both tetrahydropyranyl substituents occupy equatorial positions.

Related *trans*-selective additions of nucleophiles to C₆ substituted tetrahydropyranyl oxocarbenium ions have been previously reported. Acetal **414** was treated with propargyl trimethylsilane and Me₃SiOTf in CH₂Cl₂ to yield allene **416** diastereoselectively as the *trans* product (Scheme 2.17).²³ Lewis acid activation of the methoxy group leads to formation of oxonium ion intermediate **415**. Preferential, axial propargyl addition to the oxocarbenium ion from the top face leads to allene **416** where the nucleophile has added *trans* to the C₆ pentyl substituent. As was explained in Scheme 2.16, this reaction proceeds through chair-like transition state **415** due to its lower activation energy. This transition state also minimizes 1,3-diaxial interactions between the C₆ substituent and the incoming nucleophile.

Scheme 2.17

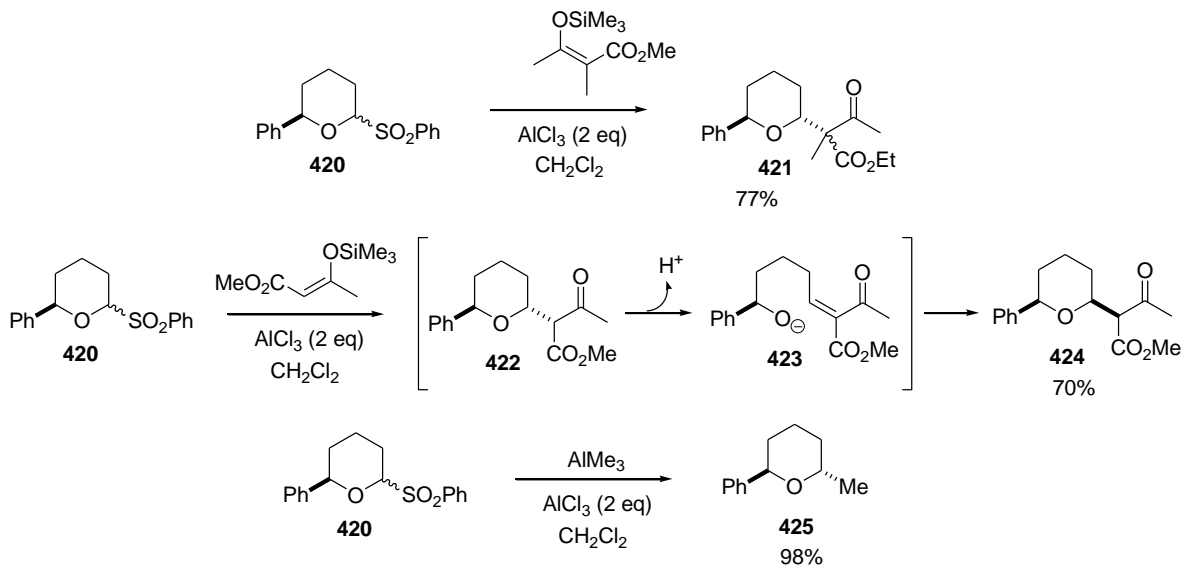


Likewise, Lucero and Woerpel discovered that allyltrimethylsilane addition to a similar oxonium intermediate formed from acetal **417** resulted in *trans*-selective tetrahydropyranyl

product **78**.²⁴ Note the similarity of these examples to our transition state **408**, which also favors *trans* addition of the nucleophile in relation to pre-existing C₆ substituents.

Addition of silyl enol ethers to 6-substituted tetrahydropyranyl 2-benzenesulfones preferentially produced the *trans* 2,6-products.²⁵ Ley demonstrated that addition of sulfone **420** to a silyl enol ether generates solely *trans* product **421** under Aluminum trichloride promotion (Scheme 2.18). Addition of the same sulfone to a trisubstituted silyl enol ether under the same conditions produced solely the *cis* product **424**. Ley also demonstrated the addition of other nucleophiles to tetrahydropyranyl benzenesulfones including addition of trimethyl aluminum to sulfone **420** to produce product **425**.

Scheme 2.18

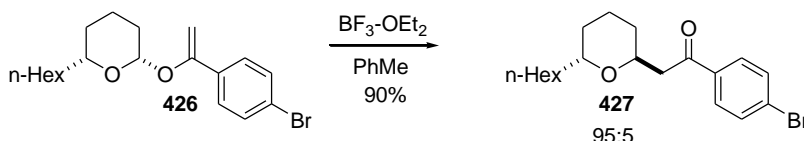


Cis product **424** arises from the equilibration of ring-opened intermediate **423**, which originates from kinetic *trans* product **422**. Ring opening followed by recyclization leads to thermodynamic 2,6-*cis* product **424**. Product **421** is not prone to isomerization because a methyl group is substituted for the acidic proton, which resided on intermediate **422**. The lack of acidic proton prevents ring opening and isomerization, providing solely the kinetic product. In all cases

production of the *trans* product predominates followed in some cases by thermodynamic equilibration to the more stable 2,6-*cis* product.

Both Ley²⁶ and Rovis²⁷ groups demonstrated related *trans*-selective rearrangement/additions of C₆ substituted tetrahydropyranyl acetals (Scheme 2.19). Acetal **427**

Scheme 2.19



was converted to the corresponding oxonium ion intermediate under Lewis acid catalysis. Subsequent addition from the opposite face of the pendant C₆ hexyl group resulted in the expected *trans*-selective product **426**. What all of these processes have in common is that they are kinetically controlled, giving rise to the *trans* product. Under thermodynamic conditions the *cis*-selective addition product predominates.¹⁵ We observed formation of the kinetically driven *trans*-addition product. This product is also the 2,6-*cis*-substituted product, which is thermodynamically favored.

2.4 Conclusions

Our lab has developed the three component coupling of exo enol ethers and activated electrophiles. This process is the first general method demonstrating the use of the exo enol ethers as nucleophiles. The reaction proceeds in good to excellent yield with both aromatic and aliphatic substituted enol ethers. The use of a highly activated electrophile is required, however, which limits the reaction scope. Use of substoichiometric levels of Lewis acid led to low product yields. Titanium(IV) chloride produced the best results when used in equimolar amounts, however, the need for stoichiometric quantities of Lewis acid is not ideal for developing related asymmetric processes which typically utilize expensive substrates.

The three component coupling process developed has demonstrated both a hydride and a carbon nucleophile to act as secondary nucleophiles toward the intermediate oxonium ion. Careful timing of secondary nucleophile addition to the oxonium ion intermediate formed is important so as to avoid byproduct formation. Typically the time required to add the secondary nucleophile is short. Presence of a preexisting C₆ substituent caused for diastereoselective addition the nucleophile. Overall this new method proved to be a useful way to synthesize tetrahydropyranyl ketides, containing up to two new quaternary oxygenated centers, from exocyclic enol ethers and activated electrophiles. This methodology we developed may have a broad impact on natural product synthesis and is most useful in creating new bonds from two carbon fragments.

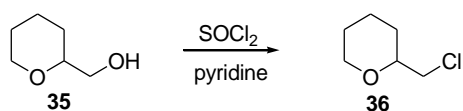
2.5 Experimental

General Methods

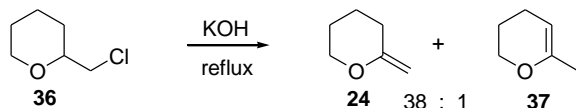
All air sensitive reactions were performed in oven dried glassware under an atmosphere of argon. Reaction solvents were dried over CaH₂ (dichloromethane and pyridine) or sodium/benzophenone ketyl (tetrahydrofuran) and were distilled just prior to use. Ethyl glyoxylate and 2,3-butanedione were distilled just prior to use. Ethyl glyoxylate was distilled according to the procedure of Evans.²⁸ All other reagents were reagent grade and were purified as necessary. Analytical thin layer chromatography was performed on EM silica gel 60 F₂₅₄ glass plates (0.25 mm). Flash column chromatography was performed using SiliaFlash P60 silica gel (40-63 μ m) from SiliCycle, Inc. ¹H NMR spectra were recorded on a Bruker Avance DPX-300 (300 MHz) spectrometer. Chemical shifts are reported in ppm, downfield from tetramethylsilane using residual CHCl₃ (δ 7.27 ppm) as the internal standard. ¹³C NMR spectra were recorded on a Bruker Avance DPX-300 (75 MHz) spectrometer with complete proton decoupling. Chemical

shifts are reported in ppm, downfield from tetramethylsilane using residual CHCl_3 as the internal standard (δ 77.0 ppm). IR spectra were obtained with a Thermo Nicolet IR-100 spectrometer on NaCl plates. Elemental analyses were performed by Complete Analysis Laboratories, Inc.; Parsippany, NJ. High resolution mass spectra were obtained using the positive ion electrospray mode on a 3-Tesla FT mass spectrometer at The Ohio State University, Columbus, OH.

Experimental Procedures:

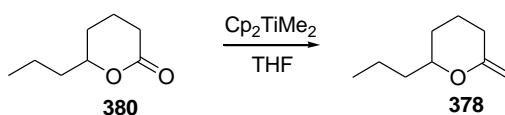


2-(Chloromethyl)tetrahydropyran 3. Chloride **3** was prepared by a known literature procedure,¹⁷ using 2-(hydroxymethyl) tetrahydropyran **379** (10.0 g, 86.2 mmol), pyridine (8.6 ml, 106 mmol), and thionyl chloride (7.6 ml, 103 mmol). The product was purified via distillation (760mmHg, 70-75°C) to give 7.26 g of chloride **3** as a colorless liquid (72% yield). The identity of this compound was established by comparing ^1H NMR data with that previously reported.²² TLC: R_f = 0.61 (hexanes: EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 4.05 (1H, m), δ 3.50 (4H, m), δ 1.90 (1H, m), δ 1.75-1.61 (5H, m).

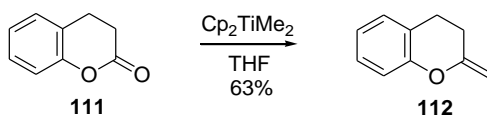


2-Methylene tetrahydropyran 2. Enol ether **2** was formed by known literature procedure,²⁹ using chloride **3** (3.86 g, 135 mmol), crushed potassium hydroxide (3.22 g, 57.3 mmol), and

oven dried, base-washed glassware. Distillation (760 mmHg, 100-110°C) yielded the desired enol ether (1.67 g) in a 60% yield in a ratio of 38:1 of **2** to **14**. The resulting product was dried over a minimal amount of sodium metal (0.10 g). The identity of enol ether **2** was established by comparing ^1H NMR data with that previously reported.²⁸ TLC: $R_f = 0.81$ (hexanes: EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 4.31 (1H, s), δ 4.04 (1H, s), δ 3.88 (2H, m), δ 2.25 (1H, m) 1.72 (4H, m).

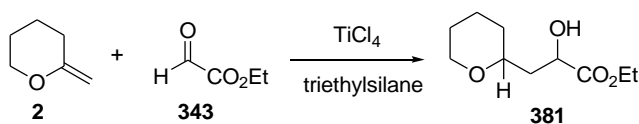


Enol Ether 378: To a solution of δ -octanolactone **380** (1.38g, 9.7 mmol) in 70 mL THF was added Cp_2TiMe_2 (39 mL of a 0.5M solution in THF, 19.5 mmol). The resulting mixture was warmed to reflux and stirred for 24 h in the dark. The solution was then cooled to room temperature, concentrated *in vacuo*, and the resulting residue was triturated with hexanes. (100 mL). The hexanes solution was filtered through celite and concentrated again. The residue was purified via flash chromatography (SiO_2 ; hexanes:triethylamine, 19:1) to afford the exocyclic enol ether **378** as a yellow oil (0.82 g, 68%). TLC: $R_f = 0.84$ (hexanes: EtOAc, 10:1). ^1H NMR (CDCl_3 , 300 MHz): δ 4.30 (1H, d, $J = 1.4$ Hz), 4.04 (1H, d, $J = 1.4$ Hz), 3.59 (1H, m), 2.25 (1H, dt, $J = 14.0, 3.8$ Hz), 2.12 (1H, m), 1.82 (1H, m), 1.74-1.32 (7H, m), 0.93 (3H, t, $J = 6.9$ Hz). ^{13}C NMR (CDCl_3 , 300 MHz): δ 160.6, 90.8, 78.9, 38.1, 30.3, 29.0, 22.7, 18.5, 14.0. IR (film): 3110, 2938, 2870, 1649 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_9\text{H}_{16}\text{O}$ ($[\text{2M}+\text{Na}]^+$): 303.2294, found 303.2288.



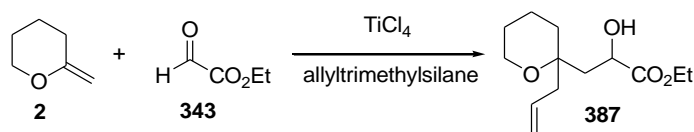
3,4-Dihydro-2-methylene-2H-1-benzopyran 112. Enol ether **112** was prepared by known literature procedure using dihydrocumarin **111** (0.96 g, 6.5mmol) and Cp_2TiMe_2 (0.5 M, 26ml).¹⁵ Purification via column chromatography (SiO_2 : 95% hexanes, 5% triethylamine) afforded the product as a colorless oil (0.60 g) in a yield of 63 %. TLC: R_f = 0.80 (Hexanes: ethyl acetate; 10:1). The identity of enol ether **112** was established by comparing ^1H NMR data with that previously reported.³⁰ ^1H NMR (CDCl_3 , 300 MHz): δ 7.17 (1H, m), 7.08 (1H, m), 6.91 (2H, m), 4.59 (1H, s), 4.17 (1H, s), 2.82 (2H, t, J = 5.1 Hz), 2.59 (2H, t, J = 5.1 Hz).

General Procedure for Three Component Coupling: To a stirred solution of the enol ether (1.00 mmol) in 5 mL CH_2Cl_2 was added the carbonyl derivative (1.20 mmol). The resulting mixture was cooled to -78°C and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH_2Cl_2 , 1.0 mmol) was added dropwise. After 5-60 minutes, triethylsilane or allyltrimethylsilane (1.00 mmol) was added dropwise and stirring continued for 5 hours at -78°C . Saturated NaHCO_3 (2 mL) was then added carefully and the mixture was warmed to room temperature. The layers were separated and the aqueous layer was extracted with additional CH_2Cl_2 (3x). The organic layers were combined, dried over MgSO_4 , filtered, and concentrated *in vacuo*.



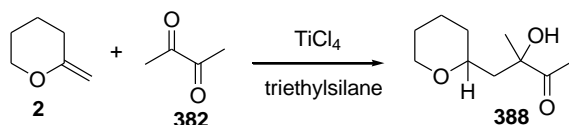
Tetrahydropyran 381: Production of tetrahydropyran **381** was conducted according to the general procedure. Ethyl glyoxylate (0.12g, 1.20 mmol), 2-methylenetetrahydropyran (0.098g, 1.00 mmol), and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH_2Cl_2 , 1.0 mmol) were combined in CH_2Cl_2 (5 mL) at -78°C . After stirring five minutes, triethylsilane (0.12g, 1.00 mmol) was added and stirring continued five more hours at -78°C . Upon workup, the residue

was purified by flash chromatography (SiO₂; hexanes:ethyl acetate, 10:1 → 5:1) to afford tetrahydropyran **381** (0.17g, 86%) as a colorless oil (1:1 mixture of diastereomers). TLC: R_f = 0.46 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 4.40 (0.5H, m), 4.32 (0.5H, m), 4.24 (1H, dq, *J* = 7.0, 2.4 Hz), 4.23 (1H, q, *J* = 7.1 Hz), 3.99 (1H, dm, *J* = 11.2 Hz), 3.92 (1H, dm, *J* = 11.2 Hz), 3.56 (1H, m), 3.55 (0.5H, d, *J* = 3.3 Hz), 3.44 (0.5H, br s), 3.42 (1H, m), 1.97 (0.5H, ddd, *J* = 14.4, 10.2, 3.2 Hz), 1.90 (1H, m), 1.82 (1H, m), 1.72 (0.5H, ddd, *J* = 14.4, 8.2, 2.6 Hz), 1.49 (3.5, m), 1.36 (0.5, m), 1.30 (3H, t, *J* = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 175.0, 174.3, 75.5, 74.8, 69.2, 68.5, 68.4, 68.2, 61.3, 61.2, 40.4, 40.1, 32.0, 31.7, 25.8, 25.7, 23.2, 23.2, 14.2, 14.1. IR (film): 3460, 2935, 2856, 1735 cm⁻¹. Anal. Calcd for C₁₀H₁₈O₄: C, 59.39%; H, 8.97%. Found: C, 59.36%; H, 8.99%.

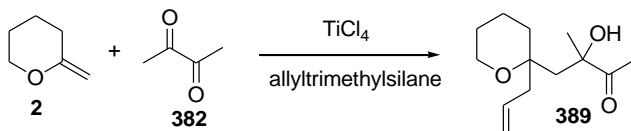


Tetrahydropyran 387: Production of tetrahydropyran **387** was conducted according to the general procedure. Ethyl glyoxylate (0.12g, 1.20 mmol), 2-methylenetetrahydropyran (0.098g, 1.00 mmol), and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH₂Cl₂, 1.0 mmol) were combined in CH₂Cl₂ (5 mL) at -78°C. After stirring five minutes, allyltrimethylsilane (0.11g, 1.00 mmol) was added and stirring continued five more hours at -78°C. Upon workup, the residue was purified by flash chromatography (SiO₂; hexanes:ethyl acetate, 15:1 → 8:1) to afford tetrahydropyran **387** (0.13g, 55%) as a yellow oil (2:1 mixture of diastereomers). TLC: R_f = 0.53 (hexanes:EtOAc, 1:2). δ 5.78 (1H, m), 5.13 (2H, m), 4.52 (1H, m), 4.23 (0.7H, m), 4.23 (1.3H, q, *J* = 7.1 Hz), 4.04 (0.3H, d, *J* = 2.8 Hz), 3.93 (0.7H, d, *J* = 2.9 Hz), 3.73 (2H, m), 2.62 (1H, dd, *J* = 14.2, 6.6 Hz), 2.47 (0.3H, dd, *J* = 14.0, 7.2 Hz), 2.31 (0.7H, dd, *J* = 14.2, 7.9), 1.96 (2H, m), 1.78 (2H, m), 1.63 (1H, m), 1.53 (3H, m), 1.30 (2H, t, *J* = 7.1 Hz), 1.29 (1H, t, *J* = 7.1 Hz). ¹³C

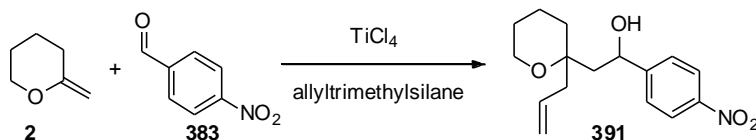
NMR (CDCl₃, 75 MHz): δ 174.5, 133.2, 118.6, 118.3, 75.5, 68.5, 68.2, 61.5, 61.3, 41.1, 40.6, 39.4, 38.2, 33.0, 31.4, 29.7, 25.4, 18.8, 18.6, 14.2. IR: 3479, 3075, 2936, 2868, 1730, 1640 cm⁻¹. HRMS (ESI) Calcd for C₁₃H₂₂O₄ ([M+Na]⁺): 265.1410, found 265.1405.



Tetrahydropyran 388: Production of tetrahydropyran **388** was conducted according to the general procedure. 2,3-Butanedione (0.10g, 1.20 mmol), 2-methylenetetrahydropyran (0.098g, 1.00 mmol), and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH₂Cl₂, 1.0 mmol) were combined in CH₂Cl₂ (5 mL) at -78°C. After stirring sixty minutes, triethylsilane (0.12g, 1.00 mmol) was added and stirring continued five more hours at -78°C. Upon workup, the residue was purified by flash chromatography (SiO₂; hexanes:ethyl acetate, 15:1 → 10:1) to afford tetrahydropyran **388** (0.147g, 79%) as a yellow oil (4:1 mixture of diastereomers). TLC: R_f = 0.47 (hexanes:EtOAc, 3:1). ¹H NMR (CDCl₃, 300 MHz): δ 4.85 (0.2H, s), 4.36 (0.8H, s), 3.98 (0.2H, dm, *J* = 11.0 Hz), 3.80 (0.8H, dm, *J* = 10.8 Hz), 3.44 (0.8H, m), 3.37 (0.2H, m), 3.24 (1H, m), 2.29 (0.6H, s), 2.22 (2.4H, s), 2.03 (0.2H, dd, *J* = 14.6, 2.0 Hz), 1.98 (0.8H, dd, *J* = 14.6, 10.1 Hz), 1.80 (1H, m), 1.75 (0.8H, dd, *J* = 14.6, 2.0 Hz), 1.71 (0.2H, dd, *J* = 14.4, 10.5 Hz), 1.48 (4H, m), 1.31 (2.4H, s), 1.27 (1H, m), 1.26 (0.6H, s). ¹³C NMR (CDCl₃, 75 MHz): δ 212.1, 73.5, 68.3, 68.0, 45.7, 44.5, 32.3, 31.9, 29.7, 26.5, 26.2, 26.0, 25.7, 24.1, 23.4, 22.9. IR (film): 3462, 2931, 2857, 1710 cm⁻¹. HRMS (ESI) Calcd for C₁₀H₁₈O₃ ([M+Na]⁺): 209.1148, found 209.1145.

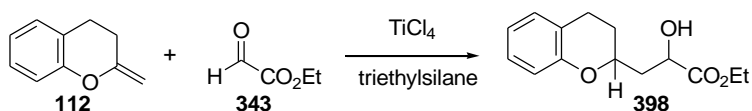


Tetrahydropyran 389: Production of tetrahydropyran **389** was conducted according to the general procedure. 2,3-Butanedione (0.10g, 1.20 mmol), 2-methylenetetrahydropyran (0.098g, 1.00 mmol), and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH₂Cl₂, 1.0 mmol) were combined in CH₂Cl₂ (5 mL) at –78°C. After stirring sixty minutes, allyltrimethylsilane (0.11g, 1.00 mmol) was added and stirring continued five more hours at –78°C. Upon workup, the residue was purified by flash chromatography (SiO₂; hexanes:ethyl acetate, 15:1 → 8:1) to afford tetrahydropyran **389** (0.12g, 51%) as a colorless oil (2:1 mixture of diastereomers). TLC: R_f = 0.46 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 5.77 (1H, m), 5.10 (2H, m), 4.99 (0.7H, s), 4.63 (0.3H, s), 3.68 (1.4H, m), 3.60 (0.6H, m), 2.59 (0.7H, dd, *J* = 14.1, 6.4 Hz), 2.42 (0.3H, dd, *J* = 14.2, 6.1 Hz), 2.32 (2.1H, s), 2.31 (0.7H, dd, *J* = 14.1, 8.0 Hz), 2.31 (0.3H, d, *J* = 14.9 Hz), 2.23 (0.9H, s), 2.22 (0.3H, dd, *J* = 14.4, 5.3 Hz), 2.20 (0.7H, d, *J* = 14.7 Hz), 1.98 (0.3H, m), 1.95 (0.7H, d, *J* = 14.7 Hz), 1.79 (0.3H, d, *J* = 14.9 Hz), 1.60 (2H, m), 1.45 (3.7H, m), 1.26 (0.9H, s), 1.22 (2.1H, s). ¹³C NMR (CDCl₃, 75 MHz): δ 215.7, 133.6, 133.4, 118.3, 118.1, 79.3, 78.7, 76.2, 75.0, 61.3, 61.3, 47.0, 45.9, 38.8, 37.8, 33.2, 32.1, 28.5, 28.4, 25.4, 25.2, 24.6, 18.9, 18.7. IR (film): 3445, 3075, 2933, 2863, 1711, 1639 cm⁻¹. Anal. Calcd for C₁₃H₂₂O₃: C, 68.99%; H, 9.80%. Found: C, 68.92%; H, 10.02%.



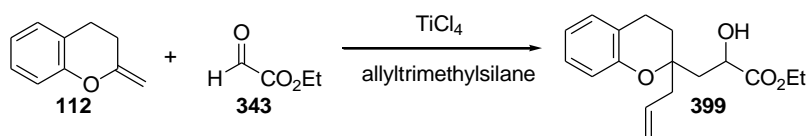
Tetrahydropyran 391: Production of tetrahydropyran **391** was conducted according to the general procedure. *p*-Nitrobenzaldehyde (0.18g, 1.20 mmol), 2-methylene-tetrahydropyran (0.098g, 1.00 mmol), and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH₂Cl₂, 1.0 mmol) were combined in CH₂Cl₂ (5 mL) at –78°C. After stirring sixty minutes, allyltrimethylsilane (0.11g, 1.00 mmol) was added and stirring continued five more hours at –

78°C. Upon workup, the residue was purified by flash chromatography (SiO₂; hexanes:ethyl acetate, 15:1 → 8:1) to afford tetrahydropyran **391** (0.095g, 38%) as a colorless oil (1:1 mixture of diastereomers). TLC: R_f = 0.44 (hexanes:EtOAc, 3:1). ¹H NMR (CDCl₃, 300 MHz): δ 8.91 (2H, dd, J = 8.9, 0.7 Hz), 7.54 (2H, m), 5.77 (1H, m), 5.18 (3H, m), 4.92 (0.4H, s), 4.87 (0.6H, s), 3.81 (2H, m), 2.59 (2H, m), 1.72 (8H, m). ¹³C NMR (CDCl₃, 75 MHz): δ 152.6, 152.5, 147.0, 133.4, 132.7, 126.5, 126.2, 123.5, 118.8, 118.6, 77.2, 76.7, 76.6, 70.3, 70.0, 61.6 (2), 47.9, 46.3, 38.5, 37.3, 33.8, 30.4, 25.4, 25.3, 18.8, 18.4. IR (film): 3438, 2943, 1520, 1346 cm⁻¹. HRMS (ESI) Calcd for C₁₆H₂₁NO₄ ([M+H]⁺): 314.1363, found 314.1361.

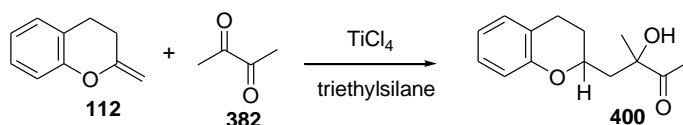


Dihydrobenzopyran 398: Production of dihydrobenzopyran **398** was conducted according to the general procedure. Ethyl glyoxylate (0.12g, 1.20 mmol), 5,6-benzo-2-methylenetetrahydropyran (0.146g, 1.00 mmol), and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH₂Cl₂, 1.0 mmol) were combined in CH₂Cl₂ (5 mL) at -78°C. After stirring five minutes, triethylsilane (0.12g, 1.00 mmol) was added and stirring continued five more hours at -78°C. Upon workup, the residue was purified by flash chromatography (SiO₂; hexanes:ethyl acetate, 9:1 → 4:1) to afford dihydrobenzopyran **398** (0.24g, 97%) as a colorless oil (1.5:1 mixture of diastereomers). TLC: R_f = 0.41 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 7.08 (2H, m), 6.84 (1.4H, m), 6.72 (0.6H, d, J = 8.1 Hz), 4.59 (0.4H, ddd, J = 9.9, 6.0, 2.9 Hz), 4.41 (0.6H, J = 9.8, 5.2 Hz), 4.35 (1H, m), 4.28 (2H, q, J = 7.2 Hz), 3.33 (0.6H, d, J = 4.5 Hz), 3.17 (0.4H, d, J = 6.0 Hz), 2.84 (2H, m), 2.18 (1.6H, m), 2.02 (1H, m), 1.82 (1.4H, m), 1.32 (1.2H, t, J = 7.4 Hz), 1.30 (1.8H, t, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 175.0, 174.7, 154.3, 154.2, 129.4, 127.0, 121.8, 121.7, 120.1, 116.7, 116.5, 72.0, 71.6, 67.6, 67.5, 61.6, 40.0, 38.8, 27.8, 27.1, 24.6, 24.3,

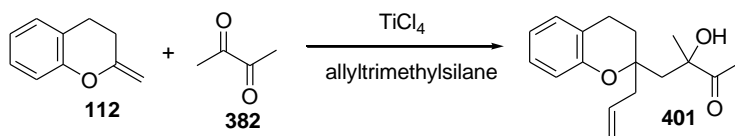
14.1, 14.0. IR (film): 3500, 3039, 2930, 2850, 1731, 1582, 755 cm^{-1} . Anal. Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_4$: C, 67.18%; H, 7.25%. Found: C, 66.97%; H, 7.12%.



Dihydrobenzopyran 399: Production of dihydrobenzopyran **399** was conducted according to the general procedure. Ethyl glyoxylate (0.12g, 1.20 mmol), 5,6-benzo-2-methylenetetrahydropyran (0.146g, 1.00 mmol), and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH_2Cl_2 , 1.0 mmol) were combined in CH_2Cl_2 (5 mL) at -78°C . After stirring five minutes, allyltrimethylsilane (0.11g, 1.00 mmol) was added and stirring continued five more hours at -78°C . Upon workup, the residue was purified by flash chromatography (SiO_2 ; hexanes:ethyl acetate, 9:1 \rightarrow 5:1) to afford dihydrobenzopyran **399** (0.28g, 96%) as a colorless oil (1:1 mixture of diastereomers). TLC: $R_f = 0.59$ (hexanes:EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 7.09 (2H, m), 6.83 (2H, m), 5.88 (1H, m), 5.16 (2H, m), 4.52 (1H, m), 4.23 (1H, q, $J = 7.1$ Hz), 4.20 (1H, m), 3.30 (0.5H, dd, $J = 14.7$ Hz), 3.26 (0.5H, d, $J = 4.8$ Hz), 2.84 (2H, m), 2.60 (0.5H, dd, $J = 14.2, 6.7$ Hz), 2.54 (1H, d, $J = 7.5$ Hz), 2.45 (0.5H, dd, $J = 14.1, 8.0$ Hz), 2.22 (0.5H, dd, $J = 14.8, 2.9$ Hz), 2.16 (0.5H, dd, $J = 14.7, 2.9$ Hz), 1.97 (3H, m), 1.28 (1.5H, t, $J = 7.1$ Hz), 1.26 (1.5H, t, $J = 7.1$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 174.9, 174.6, 152.9, 132.8, 132.7, 129.3, 127.3, 127.2, 121.0, 120.8, 120.1, 118.9, 118.6, 117.2, 117.1, 77.4, 77.2, 67.8, 67.6, 61.5, 41.2, 41.0, 40.9, 40.7, 28.7, 28.3, 21.5, 21.4, 14.0. IR: 3524, 3076, 2932, 2855, 1730, 1640, 1582, 755 cm^{-1} . Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_4$: C, 70.32%; H, 7.64%. Found: C, 70.41%; H, 7.59%.

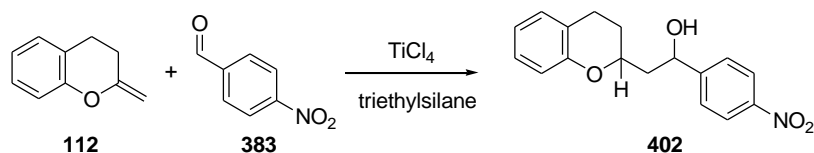


Dihydrobenzopyran 400: Production of dihydrobenzopyran **400** was conducted according to the general procedure. 2,3-Butanedione (0.10g, 1.20 mmol), 5,6-benzo-2-methylenetetrahydropyran (0.146g, 1.00 mmol), and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH₂Cl₂, 1.0 mmol) were combined in CH₂Cl₂ (5 mL) at -78°C . After stirring sixty minutes, triethylsilane (0.12g, 1.00 mmol) was added and stirring continued five more hours at -78°C . Upon workup, the residue was purified by flash chromatography (SiO₂; hexanes:ethyl acetate, 9:1 \rightarrow 4:1) to afford dihydrobenzopyran **400** (0.22g, 95%) as a yellow oil (5:1 mixture of diastereomers). TLC: R_f = 0.52 (ethyl acetate: hexanes, 1:3). ¹H NMR (CDCl₃, 300 MHz): δ 7.07 (2H, m), 6.83 (1H, m), 6.65 (1H, d, J = 8.1 Hz), 4.38 (1H, br s), 4.23 (1H, tt, J = 10.3, 2.1 Hz), 2.86 (1H, m), 2.74 (1H, m), 2.35 (0.5H, s), 2.34 (2.5H, s), 2.30 (0.83H, dd, J = 14.7, 10.3 Hz), 2.18 (0.17H, dd, J = 14.5, 3.3 Hz), 2.03 (0.17H, dd, J = 14.5, 9.1 Hz), 2.00 (0.83H, dd, J = 14.7, 2.0 Hz), 1.94 (1H, m), 1.78 (1H, m), 1.40 (3H, s). ¹³C NMR (CDCl₃, 300 MHz): δ 214.3, 211.2, 154.1, 153.6, 129.7, 129.5, 127.2, 127.1, 121.8, 121.6, 120.8, 120.3, 116.4, 116.2, 79.2, 76.7, 74.2, 71.1, 45.2, 43.8, 28.1, 27.6, 26.8, 26.1, 24.8, 24.5, 24.0. IR (film): 3464, 3022, 2928, 1710, 1582, 755 cm⁻¹. Anal. Calcd for C₁₄H₁₈O₃: C, 71.77%; H, 7.74%. Found: C, 71.83%; H, 7.82%.



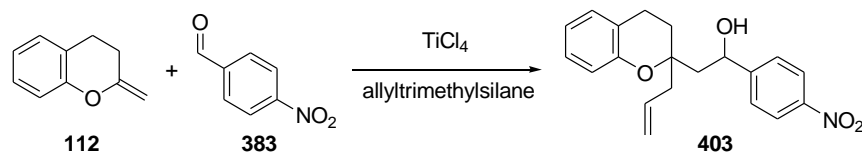
Dihydrobenzopyran 401: Production of dihydrobenzopyran **401** was conducted according to the general procedure. 2,3-Butanedione (0.10g, 1.20 mmol), 5,6-benzo-2-methylenetetrahydropyran (0.146g, 1.00 mmol), and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH₂Cl₂, 1.0 mmol) were combined in CH₂Cl₂ (5 mL) at -78°C . After stirring sixty minutes,

allyltrimethylsilane (0.11g, 1.00 mmol) was added and stirring continued five more hours at -78°C . Upon workup, the residue was purified by flash chromatography (SiO_2 ; hexanes:ethyl acetate, 12:1 \rightarrow 5:1) to afford dihydrobenzopyran **401** (0.27g, 97%) as a yellow oil (1:1 mixture of diastereomers). TLC: $R_f = 0.46$ (hexanes:EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 7.07 (2H, m), 6.84 (0.5H, m), 6.72 (0.5H, d, $J = 8.1$ Hz), 6.65 (1H, d, $J = 8.2$ Hz), 5.82 (1H, m), 5.14 (2H, m), 4.32 (0.5H, s), 4.19 (0.5H, s), 2.72 (2.5H, m), 2.53 (0.5H, d, $J = 15.2$ Hz), 2.38 (1.5H, s), 2.33 (3H, m), 2.22 (1.5H, s), 2.10 (0.5H, d, $J = 15.2$ Hz), 1.89 (0.5H, ddd, $J = 13.8, 5.8, 4.4$ Hz), 1.76 (0.5H, ddd, $J = 14.1, 6.0, 2.3$ Hz), 1.66 (0.5H, m), 1.36 (1.5H, s), 1.34 (1.5H, s). ^{13}C NMR (CDCl_3 , 75 MHz): δ 212.3, 211.2, 152.6, 152.5, 133.3, 132.8, 129.5, 129.4, 127.4, 127.2, 121.0, 120.9, 120.3, 120.2, 118.9, 118.8, 116.9, 116.6, 78.3, 78.0, 77.6, 77.3, 46.5, 45.9, 41.5, 39.6, 30.0, 28.4, 27.6, 24.4, 24.3, 21.6, 21.3. IR (film): 3458, 3075, 2930, 1709, 1583, 755 cm^{-1} . Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_3$: C, 74.42%; H, 8.08%. Found: C, 74.62%; H, 8.18%.



Dihydrobenzopyran 402: Production of dihydrobenzopyran **402** was conducted according to the general procedure. *p*-Nitrobenzaldehyde (0.18g, 1.20 mmol), 5,6-benzo-2-methylenetetrahydropyran (0.146g, 1.00 mmol), and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH_2Cl_2 , 1.0 mmol) were combined in CH_2Cl_2 (5 mL) at -78°C . After stirring sixty minutes, triethylsilane (0.12g, 1.00 mmol) was added and stirring continued five more hours at -78°C . Upon workup, the residue was purified by flash chromatography (SiO_2 ; hexanes:ethyl acetate, 7:1 \rightarrow 3:1) to afford dihydrobenzopyran **402** (0.26g, 87%) as a yellow oil (1:1 mixture of diastereomers). TLC: $R_f = 0.26$ (hexanes:EtOAc, 3:1). ^1H NMR (CDCl_3 , 300 MHz): δ 8.23 (2H,

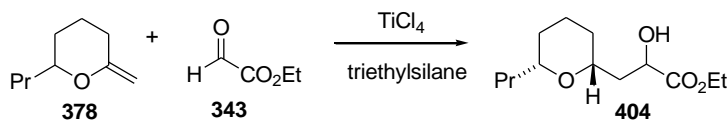
d, $J = 8.8$ Hz), 7.60 (1H, d, $J = 8.8$ Hz), 7.59 (1H, d, $J = 8.8$ Hz), 7.11 (2H, m), 6.88 (2H, m), 5.29 (0.5H, m), 5.22 (0.5H, dd, $J = 8.9, 3.8$ Hz), 4.27 (1H, m), 3.66 (0.5H, d, $J = 1.4$ Hz), 3.06 (0.5H, d, $J = 4.8$ Hz), 2.85 (2H, m), 2.03 (4H, m). ^{13}C NMR (CDCl_3 , 75 MHz): δ 154.0, 153.6, 152.0, 151.4, 147.2, 129.7, 129.7, 127.4, 127.3, 126.6, 126.4, 123.7, 121.8, 121.7, 120.9, 120.7, 116.6, 77.2, 75.9, 72.9, 72.8, 70.2, 44.8, 44.0, 28.0, 27.6, 24.6, 24.4. IR (film): 3564, 3077, 2925, 1606, 1582, 1519, 1348 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_4$ ($[\text{M}+\text{Na}]^+$): 322.1050, found 322.1049.



Dihydrobenzopyran 403: Production of dihydrobenzopyran **403** was conducted according to the general procedure. *p*-Nitrobenzaldehyde (0.18g, 1.20 mmol), 5,6-benzo-2-methylenetetrahydropyran (0.146g, 1.00 mmol), and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH_2Cl_2 , 1.0 mmol) were combined in CH_2Cl_2 (5 mL) at -78°C . After stirring sixty minutes, allyltrimethylsilane (0.11g, 1.00 mmol) was added and stirring continued five more hours at -78°C . Upon workup, the residue was purified by flash chromatography (SiO_2 ; hexanes:ethyl acetate, 12:1 \rightarrow 5:1) to afford dihydrobenzopyran **403** (0.33g, 97%) as a yellow oil (1:1 mixture of diastereomers). TLC: $R_f = 0.52$ (hexanes:EtOAc, 3:1). ^1H NMR (CDCl_3 , 300 MHz): δ 8.21 (1H, d, $J = 8.9$ Hz), 8.20 (1H, d, $J = 8.9$ Hz), 7.56 (1H, d, $J = 8.9$ Hz), 7.14 (2H, m), 6.92 (1H, m), 6.86 (1H, d, $J = 8.0$ Hz); 5.80 (1H, m), 5.24 (3H, m), 4.09 (0.5H, d, $J = 0.8$ Hz), 3.81 (0.5H, d, $J = 1.4$ Hz), 2.81 (3H, m), 2.45 (1H, m), 2.36 (1H, m), 1.94 (3H, m). ^{13}C NMR (CDCl_3 , 75 MHz): δ 152.3, 152.1, 152.1, 152.0, 132.3, 132.2, 129.7, 129.7, 127.7, 127.6, 126.5, 126.3, 123.7, 123.7, 121.1, 121.0, 119.7, 119.4, 117.5, 117.1, 79.1, 78.7, 70.1, 70.0, 47.2,

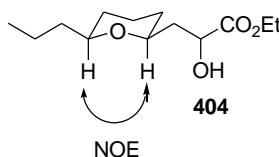
46.2, 41.2, 39.3, 30.0, 27.4, 21.5, 21.2. IR (film): 3564, 3077, 2855, 1640, 1583, 1518, 1347 cm^{-1}

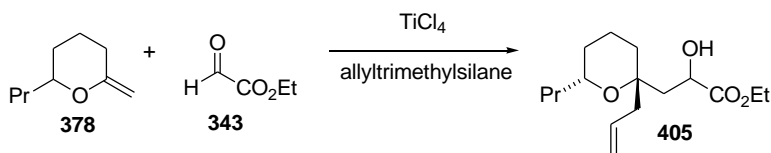
¹. Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_4$: C, 70.78%; H, 6.24%. Found: C, 71.07%; H, 6.44%.



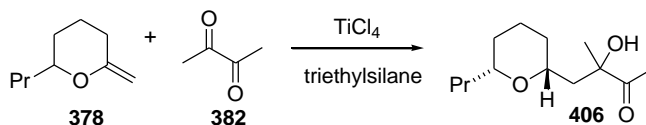
Tetrahydropyran 404: Production of tetrahydropyran **404** was conducted according to the general procedure. Ethyl glyoxylate (0.12g, 1.20 mmol), 2-methylene-6-propyltetrahydropyran (0.140g, 1.00 mmol), and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH_2Cl_2 , 1.0 mmol) were combined in CH_2Cl_2 (5 mL) at -78°C . After stirring five minutes, triethylsilane (0.12g, 1.00 mmol) was added and stirring continued five more hours at -78°C . Upon workup, the residue was purified by flash chromatography (SiO_2 ; hexanes:ethyl acetate, 15:1 \rightarrow 8:1) to afford tetrahydropyran **404** (0.19g, 77%) as a colorless oil (5:1 mixture of diastereomers). Relative stereochemistry about the tetrahydropyran was determined by NOE. TLC: $R_f = 0.41$ (hexanes:EtOAc, 3:1). ^1H NMR (CDCl_3 , 300 MHz): δ 4.42 (0.83H, dt, $J = 7.4, 3.2$ Hz), 4.36 (0.17H, m), 4.23 (2H, m), 3.94 (0.17H, d, $J = 2.8$ Hz), 3.72 (0.83H, d, $J = 7.4$ Hz), 3.62 (0.17H, m), 3.57 (0.83H, m), 3.31 (1H, m), 1.96 (1H, m), 1.80 (2H, m), 1.62-1.25 (9H, m), 1.30 (3H, t, $J = 7.1$ Hz), 0.91 (3H, t, $J = 7.3$ Hz). ^{13}C NMR (CDCl_3 , 300 MHz): δ 174.9, 77.8, 77.8, 76.4, 75.3, 70.2, 69.2, 61.2, 39.8, 39.8, 38.5, 38.5, 31.7, 31.6, 31.4, 31.2, 23.4, 23.4, 18.8, 18.7, 14.2, 14.2, 14.1. IR (film): 3480, 2932, 2863, 1733 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{24}\text{O}_4$ ($[\text{M}+\text{Na}]^+$): 267.1567, found 267.1563.

Key NOE Enhancements:



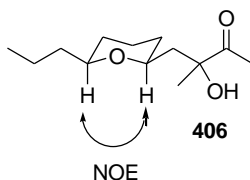


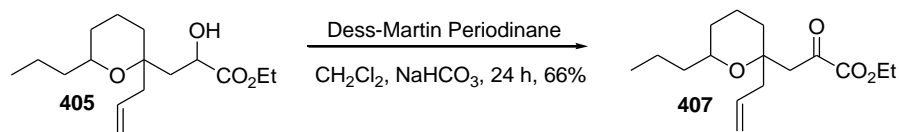
Tetrahydropyran 405: Production of tetrahydropyran **405** was conducted according to the general procedure. Ethyl glyoxylate (0.12g, 1.20 mmol), 2-methylene-6-propyltetrahydropyran (0.140g, 1.00 mmol), and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH₂Cl₂, 1.0 mmol) were combined in CH₂Cl₂ (5 mL) at -78°C. After stirring five minutes, allyltrimethylsilane (0.11g, 1.00 mmol) was added and stirring continued five more hours at -78°C. Upon workup, the residue was purified by flash chromatography (SiO₂; hexanes:ethyl acetate, 15:1 → 8:1) to afford tetrahydropyran **405** (0.19g, 67%) as a yellow oil (1:1 mixture of diastereomers). Relative stereochemistry about the tetrahydropyran ring was determined by NOE studies on the corresponding ketone. TLC: *R_f* = 0.46 (hexanes:EtOAc, 3:1). ¹H NMR (CDCl₃, 300 MHz): δ 5.73 (1H, m), 5.12 (2H, m), 4.68 (0.5H, d, *J* = 1.3 Hz), 4.58 (1.5H, m), 4.22 (1H, dq, *J* = 7.1, 0.7 Hz), 4.21 (1H, q, *J* = 7.1 Hz), 3.60 (1H, m), 2.71 (1H, m), 2.45 (0.5H, ddd, *J* = 14.1, 6.9, 1.2 Hz), 2.18 (0.5H, dd, *J* = 14.5, 8.1 Hz), 2.08 (1H, m), 1.75 (3H, m), 1.62 (3H, m), 1.36 (4H, m), 1.30 (1.5H, t, *J* = 7.1 Hz), 1.29 (1.5H, t, *J* = 7.1 Hz), 1.16 (1H, m), 0.88 (1.5H, t, *J* = 7.1 Hz), 0.87 (1.5H, t, *J* = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 173.7, 133.2, 132.9, 118.5, 118.4, 77.1, 70.4, 70.1, 69.0, 68.7, 61.0, 61.0, 43.3, 42.2, 39.0, 38.8, 38.5, 35.7, 32.7, 31.1, 31.0, 30.2, 19.1, 19.0, 18.7, 18.6, 14.2, 14.1, 14.0. IR (film): 3468, 3075, 2934, 2871, 1732 cm⁻¹. HRMS (ESI) Calcd for C₁₆H₂₈O₄ ([M+Na]⁺): 307.1880, found 307.1878.



Tetrahydropyran 406: Production of tetrahydropyran **406** was conducted according to the general procedure. 2,3-Butanedione (0.10g, 1.20 mmol), 2-methylene-6-propyltetrahydropyran (0.140g, 1.00 mmol), and titanium(IV) chloride (1.0 mL of a 1.0 M solution in CH₂Cl₂, 1.0 mmol) were combined in CH₂Cl₂ (5 mL) at -78°C . After stirring sixty minutes, triethylsilane (0.12g, 1.00 mmol) was added and stirring continued five more hours at -78°C . Upon workup, the residue was purified by flash chromatography (SiO₂; hexanes:ethyl acetate, 15:1 \rightarrow 8:1) to afford tetrahydropyran **406** (0.13g, 56%) as a colorless oil (2:1 mixture of diastereomers). Relative stereochemistry about the tetrahydropyran ring was determined by NOE. TLC: R_f = 0.65 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 5.16 (0.3H, s), 4.45 (0.7H, s), 3.50 (1H, m), 3.28 (0.3H, m), 3.15 (0.7H, m), 2.30 (1H, s), 2.24 (2H, s), 2.01 (1H, m), 1.77 (1H, dd 14.6, 1.9 Hz), 1.70 (1H, m), 1.57-1.08 (9H, m), 1.31 (2H, s), 1.25 (1H, s), 0.90 (1H, t, J = 7.3 Hz), 0.88 (2H, t, J = 7.2 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 216.5, 212.0, 80.3, 77.9, 77.6, 77.1, 76.7, 73.3, 45.4, 44.2, 38.4, 38.3, 32.0, 31.7, 31.2, 31.1, 26.3, 26.1, 24.6, 24.2, 23.5, 23.1, 18.9, 18.6, 14.2, 14.0. IR (film): 3463, 2932, 2862, 1711, cm⁻¹ HRMS (ESI) Calcd for C₁₃H₂₄O₃ ([M+Na]⁺): 251.1618, found 251.1614.

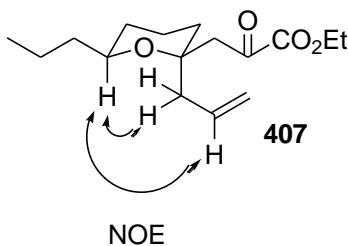
Key NOE enhancements:





Tetrahydropyran 407: To a solution of alcohol **405** (0.020g, 0.070 mmol) in CH_2Cl_2 (0.35 mL) was added Dess-Martin periodinane (0.034g, 0.081 mmol) and solid NaHCO_3 (0.029g, 0.350 mmol). The reaction mixture was stirred at rt for two hours, after which time the reaction was shown to be complete by TLC. Hexane (4 mL) was added and the resulting solution was gravity filtered to remove precipitates. The filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography (SiO_2 ; 50:1, hexanes:EtOAc) to provide tetrahydropyran **407** (0.013 g, 66%) as a colorless oil. TLC: $R_f = 0.79$ (hexanes:ethyl acetate, 3:1). ^1H NMR (CDCl_3 , 300 MHz): δ 5.79 (1H, m), 5.12 (2H, m), 4.25 (2H, dq, $J = 7.2, 1.8$ Hz), 3.50 (1H, m), 3.43 (1H, d, $J = 12.6$ Hz), 2.69 (1H, ddt, $J = 14.4, 6.1, 1.4$ Hz), 2.44 (1H, d, $J = 12.6$ Hz), 2.27 (1H, dd, $J = 14.4, 8.3$ Hz), 1.66 (2H, m), 1.56 (2H, m), 1.50 (1H, dm, $J = 14.0$ Hz), 1.38 (1H, m), 1.36 (3H, t, $J = 7.2$ Hz), 1.25 (3H, m), 1.09 (1H, m), 0.87 (3H, t, $J = 7.0$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 195.4, 162.2, 133.2, 118.5, 76.5, 69.9, 61.9, 47.8, 38.8, 37.3, 31.6, 30.9, 19.2, 18.5, 14.1, 13.9. IR (film): 3077, 2937, 2871, 1728, 1640 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{26}\text{O}_4$ ($[\text{M}+\text{Na}]^+$): 305.1723, found 305.1718.

Key NOE enhancements:



2.6 References

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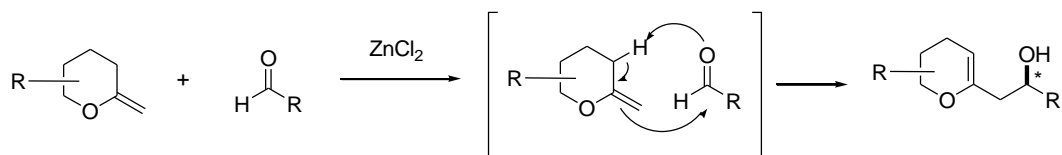
Chapter 3: Carbonyl-Ene Reactions of Exocyclic Enol Ethers: Chiral Induction Studies

3.1 Overview

Since its discovery nearly seventy years ago, the ene reaction has found abundant utility in making carbon-carbon bonds. Carbonyl-ene reactions are one segment of this chemistry and combine olefins with oxygenated double bonds. Herein we discuss the carbonyl-ene reaction of exocyclic enol ethers, again demonstrating their inherent nucleophilicity. Specifically chiral induction from substrate to ene product is studied on 2-methylenetetrahydropyrans with one or two pre-existing stereocenters.

This chapter will briefly review carbonyl-ene chemistry, focusing on diastereoselective processes. Previous research in this field focused on the production of racemic mixtures of β -hydroxydihydropyrans from carbonyl-ene reactions of exocyclic enol ethers and a variety of aldehydes and ketones. The utility of this carbon-carbon bond forming transformation would be enhanced through control of the newly formed stereocenter. Chiral induction from the enol ether to the resulting product is discussed here. Seven new substituted 2-methylenetetrahydropyrans were synthesized, three enol ethers containing one chiral center and four possessing two stereocenters. These exo enol ethers were subsequently subjected to carbonyl-ene conditions, which involved catalytic zinc chloride and aldehydes with a range of reactivity (Scheme 3.1). The extent of chiral induction these enol ethers have on the resulting β -hydroxydihydropyran products is discussed.

Scheme 3.1

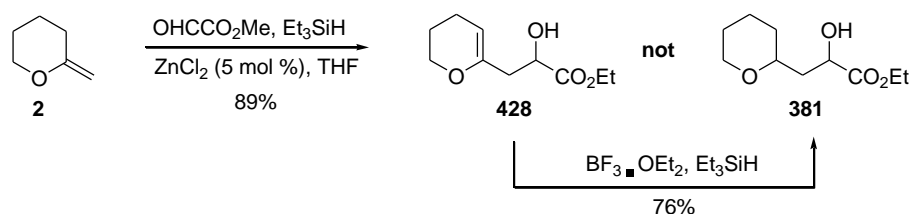


3.2 Background and Significance

Previous work in our lab demonstrated the inherent nucleophilic nature of 2-methylene-tetrahydropyrans through their use in the three component coupling with electron deficient aldehydes and secondary nucleophiles. This coupling reaction successfully produced synthetically useful β -hydroxy-tetrahydropyranyl ketides, but only with the use of titanium(IV) chloride as the Lewis acid. Other Lewis acids were screened, but failed to yield the desired tetrahydropyran product. Although this is a useful method for the introduction of tetrahydropyran moieties, the reaction is somewhat limited in scope and utility for natural product synthesis. Ultimately, the goal was to find a more general method towards tetrahydropyranyl ketide synthesis that would take place under mild conditions.

Further evaluation of reaction conditions associated with the three component coupling reaction led to the discovery that zinc chloride promoted a similar process, the ene reaction of 2-methylenetetrahydropyrans with aldehydes and activated ketones. Even in the presence of triethylsilane, carbonyl-ene products were formed, which upon treatment with $\text{BF}_3 \cdot \text{OEt}_2$ and triethylsilane, provided tetrahydropyran products (Scheme 3.2). This transformation holds

Scheme 3.2



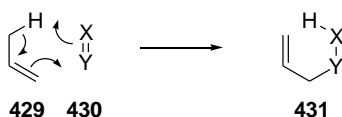
advantage over the three component coupling reaction in that milder reaction conditions are used. Zinc(II) chloride, a mild Lewis acid, promoted minor carbonyl activation without decomposition of the labile exo enol ether. The use of a mild Lewis acid allows the carbonyl to participate in the reaction and abstract a hydrogen, six atoms away, thus leading to the carbonyl-

ene product. A strong Lewis acid like titanium(IV) chloride binds tightly to the carbonyl oxygen and prevents oxo-addition until work-up. The formation of these ene adducts inspired further investigation.

The Carbonyl-Ene Reaction: Mechanism and Transition States of Thermal and Lewis Acid Promoted Processes

The ene reaction has proven to be a valuable carbon-carbon bond-forming technique since Alder highlighted it in his 1943 publication¹ and has been studied on a wide variety of substrates.² Ene reactions are defined as pericyclic processes between an olefin possessing an allylic hydrogen **429** and an enophile **430** that contains an electron deficient multiple bond (Scheme 3.3). This reaction involves the transfer of the allylic hydrogen to the enophile oxygen, an allylic shift of the ene olefin, and bonding between the two alkenyl termini.

Scheme 3.3

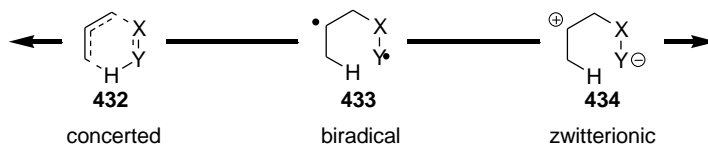


Although mechanistically similar to the Diels-Alder reaction, the ene reaction possesses a higher activation energy when comparing bond dissociation energies between the two systems. The Diels-Alder mechanism requires breakage of only pi bonds. On the other hand, two of the electrons involved in the ene pericyclic process originate from a sigma bond. Sigma bonds possess higher bond dissociation energies than pi bonds, resulting in higher overall reaction activation energies. These two reactions are nonetheless mechanistically similar and with use of certain substrates ene byproducts can be detected in the Diels-Alder reaction and vice versa.

The ene reaction mechanism ranges from a concerted (**432**) to a zwitterionic (**434**) process based on the substrates at hand (Scheme 3.4). If simultaneous bond making at both ends

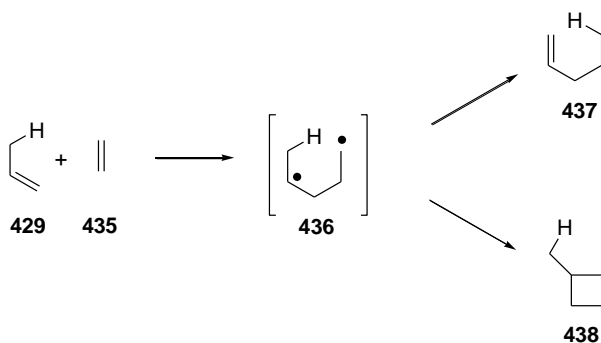
of the ene terminus is geometrically unfavorable and to a lesser extent if radical intermediates can be stabilized, a stepwise radical mechanism can also prevail (**433**).^{2a} In the stepwise biradical approach radical intermediates like **436** are formed, which inevitably leads to some cyclobutane

Scheme 3.4



438 formation (Scheme 3.5).³ Thus the presence of cyclobutane derivatives indicates a radical stepwise mechanism. Ene reactions of substrates without strained transition states, however, typically follow a truly concerted course in the case of thermal, all carbon systems, or a partial ionic mechanism.

Scheme 3.5

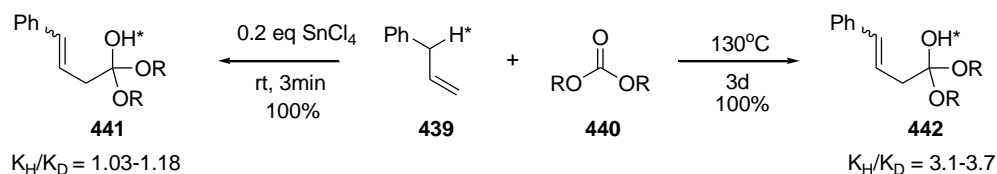


Whether the mechanism is concerted, stepwise, or somewhere in-between, ene reactions involving Lewis acids undoubtedly develop a positive charge to some extent on the ene component.⁴ Ene reactions that exhibit any level of concerted mechanism, proceed through a single-barrier process, which can yield products with good stereoselectivity. The purely stepwise cationic method, on the other hand, proceeds through a cationic intermediate. Either

formation of the cationic intermediate or the secondary hydride transfer can be rate determining. In the latter case, creation of the cationic intermediate is reversible.

Deuterium isotope effects can aid in determining the type of mechanism the ene reaction proceeds through. Ene reactions of deuterated ene **439** and oxomalonate **440** were studied under both thermal and Lewis acid catalyzed conditions (Scheme 3.6).⁵ A primary deuterium isotope

Scheme 3.6

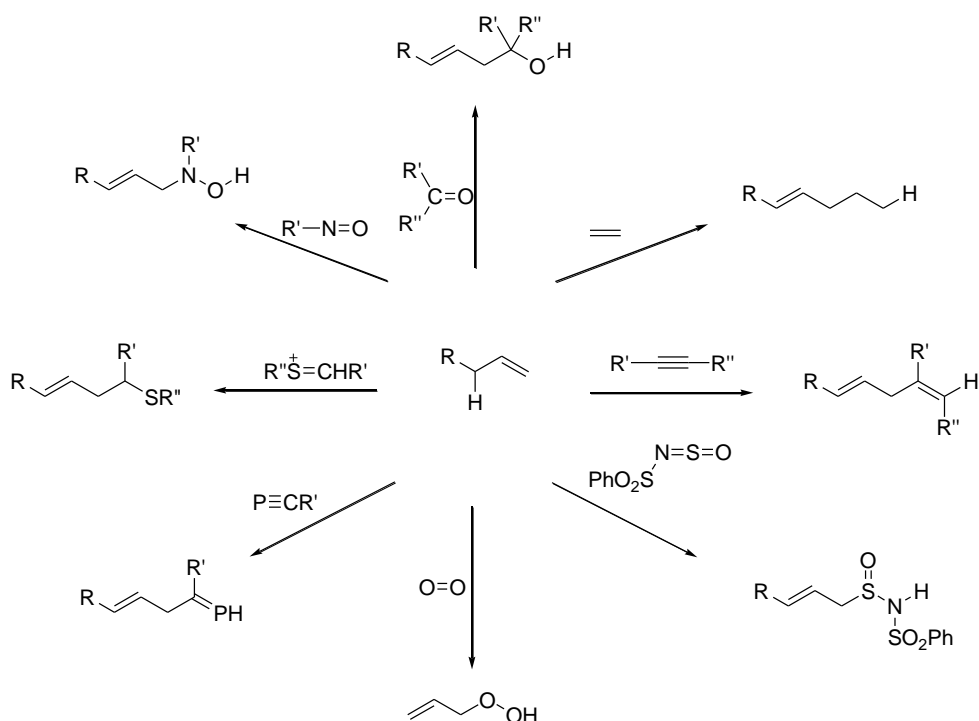


effect was observed for the thermal reaction. This result arises from CH bond-breakage in the transition state, indicating a concerted mechanism. The minimal primary isotope effect observed for the Lewis acid catalyzed ene reaction, however, indicates a concerted mechanism in which CH bond breakage has only minimally progressed in the transition state. The transition state would possess a partial cationic charge associated with the ene component. If a truly cationic mechanism prevailed no primary isotope effect would be expected. Without these kinetic studies, however, it is not always clear exactly what mechanism the ene reaction follows for different substrates.

A number of different enophiles have been utilized in ene reactions (Scheme 3.7). These include substrates from four different groups: carbon-carbon multiple bonds (olefinic,⁶ acetylenic,⁷ an benzyne⁸), carbon-hetero multiple bonds (C=O,⁹ C=N,¹⁰ C=S,¹¹ and C≡P¹²), hetero-hetero multiple bonds (N=N,¹³ O=O,¹⁴ Si=Si,¹⁵ N=O,¹⁶ and S=O¹⁷), cumulene systems (N=S=O,¹⁸ N=S=N,¹⁹ C=C=O,²⁰ C=C=S,⁸ and O=S=O²¹), as well as other charged pi systems (C=N⁺,²² C=S⁺,²³ C≡N⁺,²⁴ and C≡O⁺²⁵).

Aldehydes, ketones, and glyoxylates are commonly used in carbonyl-ene reactions and will be the only substrates examined in any detail due to their relevance to the reactions discussed herein. The carbonyl enophiles are more reactive than olefins in the ene reaction, and these types of reactions are effectively promoted by Lewis acids. The advantages to Lewis acid catalyzed processes over thermal are two fold, and the differences associated with these two processes are discussed herein. The use of a metal catalyst provides possible asymmetric control over the reaction, while avoiding undesired byproduct formation often accompanied with high temperatures.

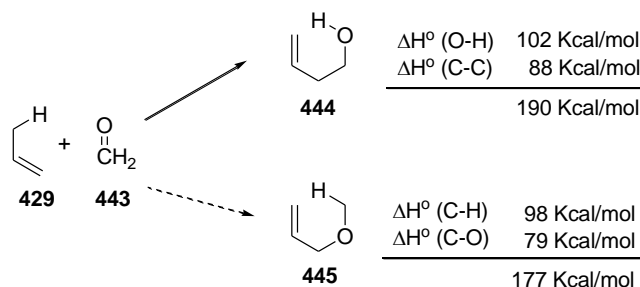
Scheme 3.7



Alcohols **444** are exclusively produced from carbonyl-ene reactions rather than the corresponding ethers based on thermodynamic and stereoelectronic grounds. Ether **445** formation is avoided due to the greater gain in bond energy for the reaction (Scheme 3.8).²⁶ The carbon-oxygen double bond is also naturally polarized such that the carbon is electrophilic and

set up to accept a bond from the electron-rich ene. Coordination of Lewis acids to the oxygen portion of the carbonyl further polarizes the carbon-oxygen bond and activates the carbon center for nucleophilic addition, thus avoiding the need for a thermal process.

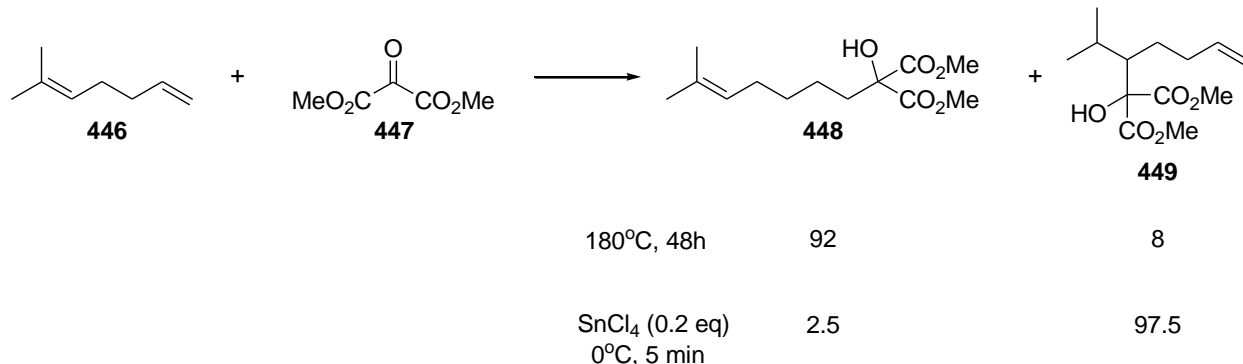
Scheme 3.8



The large activation energy associated with the ene reaction lends to its facilitation with either thermal or Lewis acid conditions. The two processes differ in mechanism, transition state, and the major diastereomer products formed. As previously mentioned, the mechanism of the ene reaction may differ for thermal based processes versus Lewis acid promoted ones. The thermal reaction typically undergoes a completely concerted mechanism while the Lewis acid-promoted reaction contains a partial cationic intermediate or transition state.

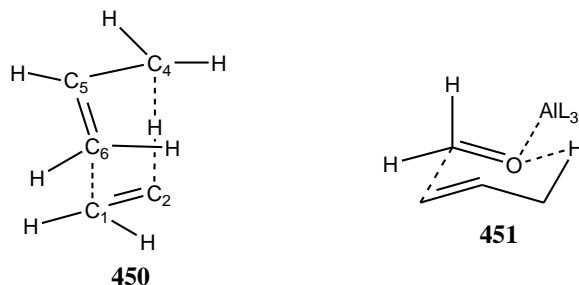
Based upon their mechanistic differences, the thermal ene reactions generally produce products that stem from sterically accessible olefins and allylic hydrogens whereas Lewis acid-promoted processes produce products based on reaction intermediate stability. For example, when diene **446** is added to dimethyl oxomalonate **447** under thermal conditions, product **448** prevails (Scheme 3.9).²⁷ The more sterically accessible terminal olefin preferentially reacts. Alternatively, the same reactants produce primarily product **449** under Lewis acid catalyzed conditions. Here, a partial positive charge develops on the ene reactant. Progression to this intermediate is rate determining and therefore addition occurs from the tri-substituted olefin, preferentially producing product **449** as a result.

Scheme 3.9



The thermal ene reaction develops an early envelope-like transition state structure **450** between the ene and enophile substrates (Figure 3.1).²⁸ Although planar in both the reactants and products, in this transition state C₅ distorts slightly from planarity to maximize p orbital overlap between the C₅ carbon and those p or slightly hybridized p orbitals of C₆ and C₄. Through this orientation, the C₅ carbon is able to maximize its pi overlap with C₆ until the pi bond between C₅ and C₄ has significantly developed. Notably, substitution of formaldehyde for ethylene resulted in little change in this transition state conformation. Alternatively, in the case of carbonyl-ene reactions, Lewis acid promotion results in chair-like late transition states **451**, which minimize torsional and steric strain in six-membered processes.²⁹

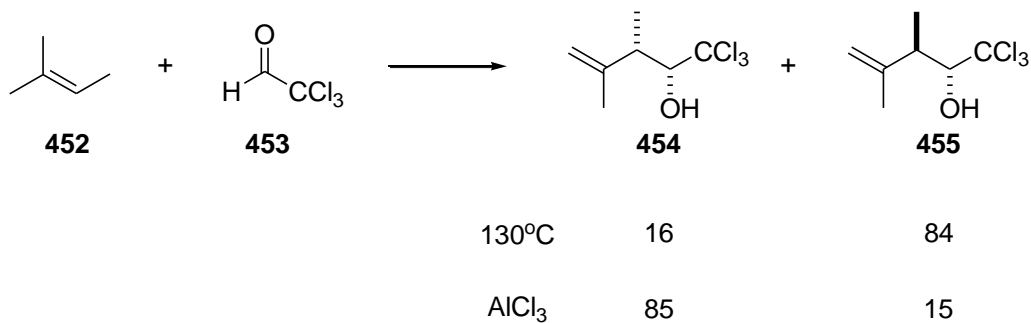
Figure 3.1



The difference in transition state between the two ene reactions lends to variations in their diastereocontrol. The thermal carbonyl-ene reaction of 2-methyl-2-butene **452** with chloral **453**

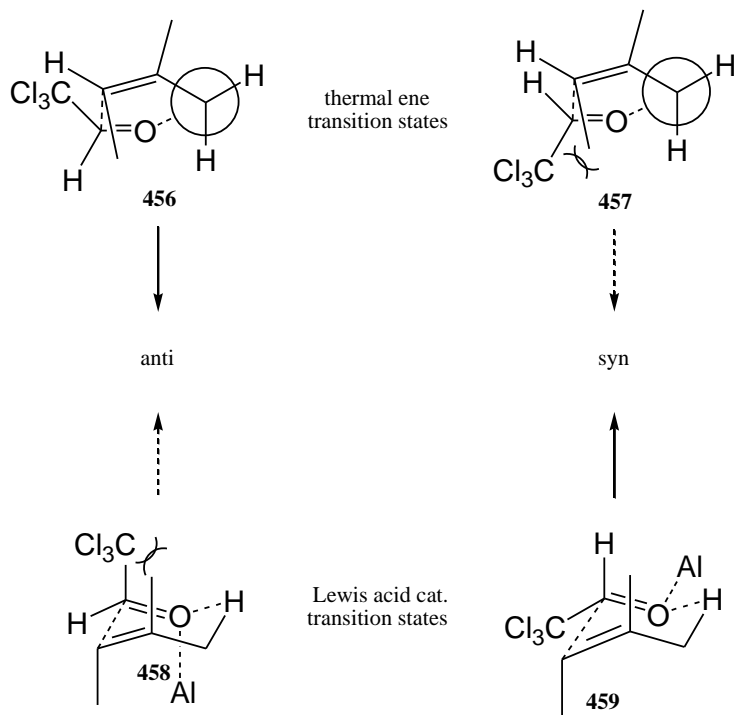
results in production of anti isomer **455** (84%) versus production of primarily the syn isomer **454** (85%) under Lewis acid catalysis (Scheme 3.10).³⁰ The thermal reaction proceeds through either envelope-like transition state **456** or **457** (Scheme 3.11). Transition state **456**

Scheme 3.10



predominates due to the steric repulsion experienced between the methyl and trichloro groups within transition state **457**, therefore favoring formation of the anti ene diastereomer. The Lewis

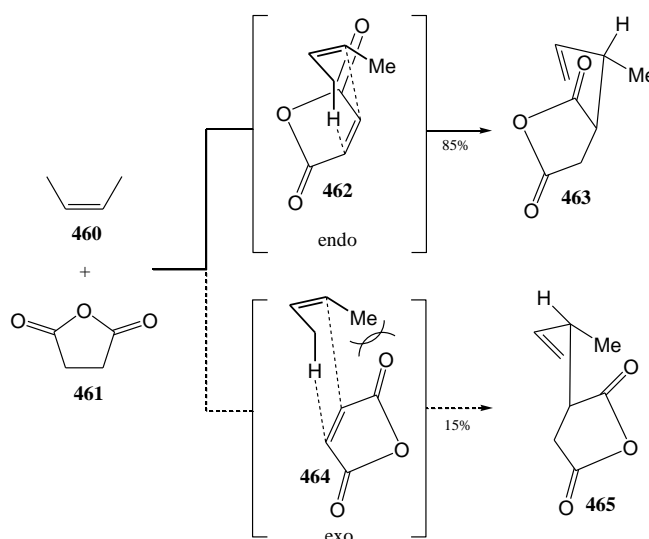
Scheme 3.11



acid catalyzed reaction, which undergoes a chair-like transition state, favored syn product formation because 1,3-diaxial steric repulsions are avoided. Thus, thermal and Lewis acid catalyzed processes have been proven to preferentially produce products of opposite stereochemistry based solely upon the transition state geometry.

Furthermore internal asymmetric induction may be observed in ene systems where favorable secondary orbital overlap can occur in the transition state. Berson demonstrated the thermal ene reaction between maleic anhydride and *cis*-2-butene to proceed preferentially through endo transition state **462** (Scheme 3.12).³¹ Like the Diels Alder reaction, the activation

Scheme 3.12

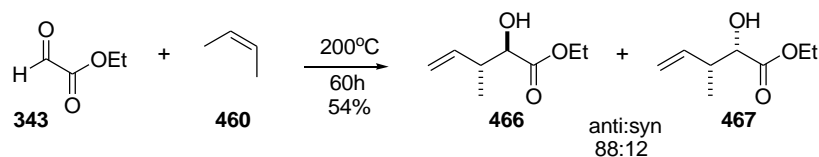


energy of the endo transition state is reduced by secondary p-orbital overlap between the ene and enophile. The exo transition state does not experience the same stabilization and leads to a product with the opposite relative stereochemistry. The reaction of maleic anhydride with *cis*-2-butene resulted in production of products **463** and **465** in a 85:15 ratio, in favor of the endo product. *Trans*-2-butene, on the other hand, resulted in a 43:57 ratio of products. A decrease in selectivity is observed due to competing steric influences associated with the *trans* methyl group.

Ene reactions of *cis* and *trans* decanes delivered similar results, indicating again that the endo transition state can be sensitive to steric effects.³²

The carbonyl-ene reactions of ethyl glyoxylate **343** were studied under both thermal and Lewis-acid catalysis to determine endo/exo transition state bias.³³ The reaction of ethyl glyoxylate and *cis*-2-butene at 200°C resulted in a 88:12 diastereomeric mixture of products favoring anti isomer **466**, which resulted from the endo transition state (Scheme 3.13). The reaction of *trans*-2-butene again resulted in lower product selectivity (36:64) due to competing steric interactions, but nonetheless produced endo, syn product **467** as the major isomer. Promotion of the carbonyl-ene reaction of *cis*-2-butene with Fe(III) chloride produced the desired ene adducts, favoring the anti isomer, but with much lower selectivity (58:42) than the thermal reaction.

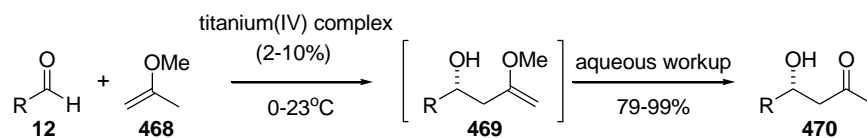
Scheme 3.13



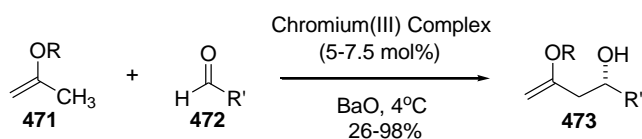
Carbonyl-Ene Reactions of Enol Ethers

Ene reactions of enol ethers are limited in the literature to the asymmetric work of Careirra³⁴ and Jacobsen.³⁵ Careirra combined aldehydes and 2-methoxypropene **468** along with a chiral titanium(IV) binol complex to provide the β-hydroxyketones **470** in good to excellent yields after aqueous acidic workup (Scheme 3.14). Similarly, Jacobsen demonstrated both 2-methoxypropene and the TMS equivalent to react with aldehydes under chromium(III) complex catalysis (Scheme 3.15). The work of these two authors focuses specifically on enantioselective examples and will be discussed later in this work (Tables 3.6 and 3.7).

Scheme 3.14



Scheme 3.15



Carbonyl-ene reactions involving exocyclic enol ethers, the focus of this chapter, are underutilized in the literature. Only one general method has been established,³⁶ and other examples are restricted to one report where product formation is driven by aromatization³⁷ and an instance of byproduct formation from a Diels-Alder reaction.³⁸

In 2005 Miles *et al.*³⁹ developed a strategy towards the synthesis of β-hydroxy furans via the carbonyl-ene reaction of 2-methylene-2,5-dihydrofuran **474** with various enophiles. A selection of their results is included in Table 3.1. The reaction with highly activated enophile

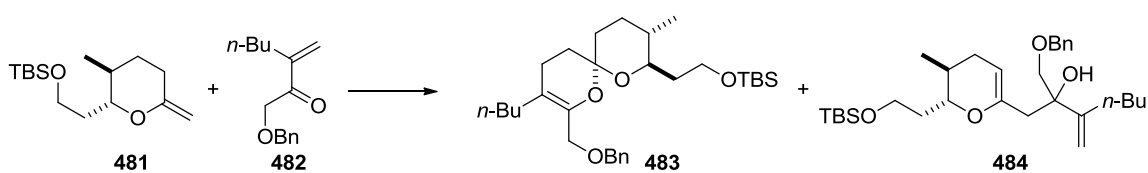
Table 3.1: Carbonyl Ene Reactions of 2-Methylene-2,5-dihydrofuran

Entry	Substrate	Temp	Catalyst	Product	Yield (%)
1	 343	0°C	none	 476	89
2	 477	22°C	ZnCl ₂	 478	78
3	 479	22°C	Yb(fod) ₃	 480	93

ethyl glyoxylate **343** proceeded in excellent yield without Lewis acid activation (entry 1). Good to excellent yields were obtained for non-activated enophiles **477** and **479** as well through Lewis acid catalysis with both zinc(II) chloride and Yb(fod)₃ (entries 2 and 3). Although this methodology presents an efficient method toward stereoselective β -hydroxy furan synthesis, it varies greatly from the carbonyl-ene methodology of simple exo enol ethers in that aromatization drives the reaction forward.

Rizzacasa has demonstrated the formation of β -hydroxy dihydropyran **484** as a byproduct of the Diels Alder reaction.⁴⁰ Combination of enol ether **481** with enone **482** resulted in formation of hetero-Diels Alder product **483** and ene biproduct **484** (Table 3.2). Under purely

Table 3.2: Pericyclic Reaction Conditions of Enol Ether 481



Entry	Additive (mol %)	Solvent	Temp (°C)	Time (h)	Yield (%)	ratio (483:484)
1	K ₂ CO ₃ (50)	toluene	110	24	11	1:0
2	K ₂ CO ₃ (50)	neat	110	24	26	1:0
3	Eu(fod) ₃ (15)	MeCN	0	48	35	1:1.3
4	Eu(fod) ₃ (15)	neat	0	72	59	2:1

thermal conditions only the desired Diels Alder product was detected albeit in low yield (entry 1). A slight improvement in yield was obtained by performing the reaction neat (entry 2). The authors then turned to Lewis acid catalyzation with lanthanide catalyst Eu(fod)₃ to improve the yield of Diels Alder adduct **483**, however ene adduct **484** also resulted as a mixture of diastereomers in a 1:1.3 ratio respectively (entry 3). Again performing this reaction neat resulted

in a reasonable yield of Diels Alder adduct **483** such that it could be later transformed into reveromycin A.

Recently, a general method has been developed in the Totah group that demonstrates the ability of exocyclic enol ethers to undergo the carbonyl-ene reaction.⁴¹ This research combined exocyclic enol ethers with a variety of enophile substrates to provide β -hydroxy dihydropyrans in excellent yields under zinc(II) chloride catalysis. The reaction benefits from low catalyst loading, use of equimolar quantities of enol ether and enophile, and wide enophile substrate scope as depicted in Table 3.3.

Highly activated aldehyde ethyl glyoxylate **343** reacted quickly in excellent yield with low catalyst loading (entry 1). Likewise, the activated ketone ethyl pyruvate **369** resulted in excellent yields of product **488**, although longer reaction time (15 h) was required (entry 2). Aromatic aldehydes bearing both electron withdrawing (**383**, entry 3) and electron donating (**491**, entry 5) groups worked well as enophile components, although the non-activated aromatic aldehydes **479** and **491** required longer reaction times and higher catalyst loadings (entries 4 and 5). Only moderate yields were obtained with conjugated aldehyde **493** (entry 6). Excellent yields were obtained for the carbonyl-ene reaction with aliphatic aldehydes octyl aldehyde **496** and cyclohexylaldehyde **497** (entries 7 and 8).

As demonstrated, reactive enophile components range from highly activated (**343**) to somewhat deactivated aldehydes (**491**) and include activated ketones (**369**). Secondly, other aromatic and C₃-substituted exocyclic enol ethers were screened for use in the carbonyl-ene reaction and the results are shown in Tables 3.4 and 3.5. Both the dihydrocoumarin derived enol ether **112** and the 6,6-diphenyl exocyclic enol ether **499** reacted quickly to produce ene adducts in excellent yields with the use of highly activated ethyl glyoxylate **343** (entries 1 and 2).

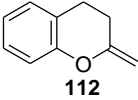
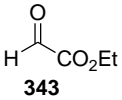
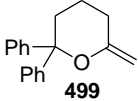
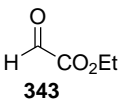
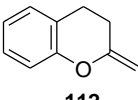
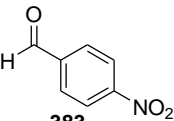
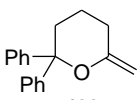
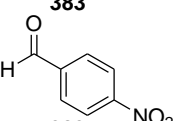
Table 3.3: Carbonyl-Ene Reactions of 2-Methylenetetrahydropyran

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Entry	Enophile	Time	mole % ZnCl ₂	Yield	Product
1	343	2 hr	5	92%	487
2	369	15 hr	5	90%	488
3	383	2 hr	5	90%	489
4	479	24 hr	20	93%	490
5	491	24 hr	20	99%	492
6	493	24 hr	5	69%	494
7	495	12 hr	5	93%	496
8	497	24 hr	5	85%	498

Coupling with *p*-nitrobenzaldehyde, a lesser activated enophile component, resulted in high yield for enol ether **499** (entry 4), however enol ether **112** required a longer reaction time and higher catalyst loading to produce moderate yields of the desired ene adduct (entry 3).

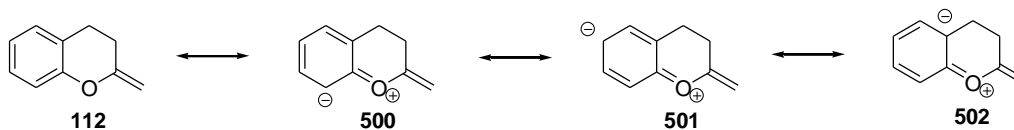
Enol ether **112** suffers from deactivation by the aromatic ring, which pulls electron density from the ene component through resonance (Scheme 3.16). With highly activated enophile substrates, use of deactivated exocyclic enol ether **112** had little effect on yield. The

Table 3.4: Carbonyl-Ene Reactions of Substituted Exocyclic Enol Ethers

Entry	Enol Ether	Enophile	Time	mole % ZnCl ₂	Yield
1	 112	 343	1 hr	5	91%
2	 499	 343	1 hr	5	90%
3	 112	 383	72 hr	20	48%
4	 499	 383	6 hr	5	99%

reaction of enol ether **112** with less reactive enophiles resulted in lower product yields, in the case of *p*-nitrobenzaldehyde **383** (entry 3), or no product production in the case of non-activated octyl aldehyde **495**.

Scheme 3.16



Exo enol ethers bearing C₃ substitution increase the steric bulk at the reaction center. Therefore these enol ethers were studied to determine the effect of C₃ substitution on the carbonyl-ene reaction rate. Reaction of the C₃-substituted enol ethers **503** and **504** resulted in the desired ene adducts in moderate to excellent yields (Table 3.5). Combination with highly activated ethyl glyoxylate **343** resulted in excellent yields (entries 1 and 2). However, the reaction rate of C₃-substituted enol ethers **503** and **504** decreased upon subjection to *p*-nitrobenz-

Table 3.5: Carbonyl-Ene Reactions of C₃-Substituted 2-Methylenetetrahydropyrans

Entry	Enol Ether	Enophile	Time	mole % ZnCl ₂	Yield
1			1 hr	5	97%
2			12 hr	5	93%
3			24 hr	20	72%
4			22 hr	5	95%
5			24 hr	20	56%

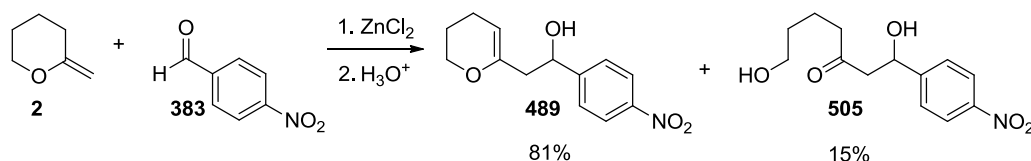
aldehyde **383**. Both enol ethers required longer reaction times (entries 3 and 4) compared to 2-methylenetetrahydropyran **2** (Table 3.3, entry 3) and in the case of enol ether **503**, a higher catalyst loading.

The decrease in reaction rate indicates that the carbonyl-ene mechanism is concerted. As previously discussed,²⁷ the rate of the concerted ene reaction is affected by sterics at the reaction center. Therefore the decrease in reaction rate seen going from 2-methylenetetrahydropyran, which is an unhindered substrate, to 3-methyl or 3-allyl-2-methylenetetrahydropyran, sterically hindered substrates, indicates a concerted reaction mechanism. To support this data, exo enol ether **504** was additionally studied with non-activated octyl aldehyde **495** (Table 3.5, entry 5). Again this reaction demonstrates a decrease in the reaction rate using C₃-substituted enol ethers.

Both longer reaction time and a higher catalyst loading were required for modest yields of the ene adduct as compared to the 2-methylenetetrahydropyran example (Table 3.3, entry 7).

This carbonyl-ene reaction of exocyclic enol ethers yields similar products as the three-component coupling methodology outlined in chapter 2. The dihydropyran products of the carbonyl-ene reaction, however, are prone to hydrolysis, and therefore the best reaction yields were obtained when purification via column chromatography immediately followed reaction completion. An aqueous workup was avoided because the addition of water facilitates the production of open-chain hydrolyzed byproduct **505** (Scheme 3.17).⁴² Nonetheless the advantages of the carbonyl-ene methodology over the three component coupling reaction include the use of catalytic amounts of a mild Lewis acid (5-20 mol%), a wider substrate scope (use of non-activated aldehydes and ketones), and room temperature reaction conditions.

Scheme 3.17



The carbonyl-ene reaction of enol ethers results in formation of a new stereogenic center at the hydroxy carbon. Control of this newly formed chiral center has importance in the reaction's application to natural product synthesis. Methods to induce stereocontrol in the ene reaction include enantioselective chiral catalysis and diastereoselective chiral induction derived from chiral reactants. The latter is the focus of this work.

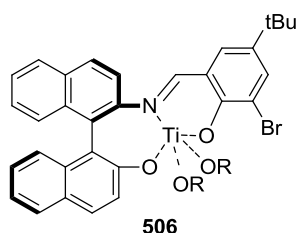
Asymmetric Carbonyl-Ene Reactions of Enol Ethers

Enantioselective carbonyl-ene reactions have been extensively studied through use of chiral catalysis.⁴³ These asymmetric ene reactions represent a large topic that lies outside of the

scope of the current discussion, therefore this discussion will be restricted to enantioselective carbonyl-ene reactions of enol ethers.

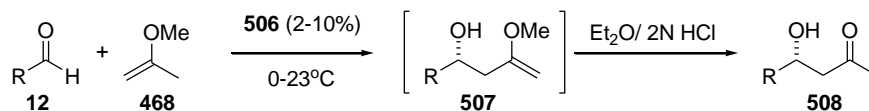
Careirra first demonstrated the use of enol ethers in carbonyl-ene reactions toward the manufacture of β -hydroxy ketones.⁴⁴ Catalyzation of this process by titanium(IV) complex **506** (Figure 3.2) led to the desired chiral enol ether intermediates **507**, which upon aqueous acidic workup produced the β -hydroxyketone products in good to excellent yields (Table 3.6). The 2-methoxypropene enol ether was used as solvent in these cases as the reaction would not proceed

Figure 3.2



upon dilution. Excellent enantioselectivities were obtained with use of non-hindered enophiles such as acetylenic and aliphatic aldehydes (Table 3.6, entries 1 and 2). Lower selectivities were observed using aromatic aldehydes (entries 3 and 4).

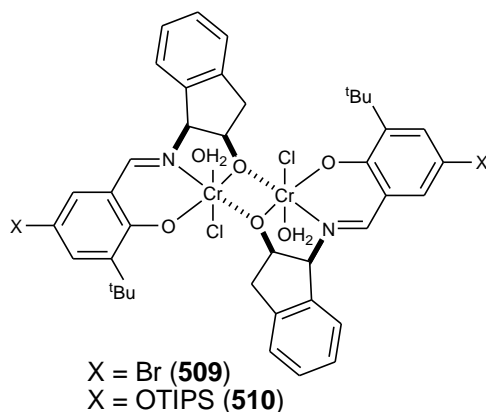
Table 3.6: Carreira Carbonyl-Ene Reactions of Enol Ethers



Entry	Aldehyde	Temp.	Yield	ee
1	Ph—C≡C—CHO	0°C	99%	91%
2	Ph—CH ₂ CH ₂ —CHO	0-23°C	98%	90%
3	PhCHO	0-23°C	83%	66%
4	<i>o</i> -C ₆ H ₁₁ CHO	0-23°C	79%	75%

Jacobsen later developed an ene methodology utilizing chiral tridentate schiff base chromium(III) complexes **509** and **510** (Figure 3.3) as catalysts in the ene reaction of both enol

Figure 3.3



ethers and silyl enol ethers.⁴⁵ Pre-stirring the catalyst with desiccant barium oxide for five hours maximized enantioselectivities for this reaction. The reaction of 2-methoxypropene **468** was successful in producing carbonyl-ene products with aromatic aldehydes as enophile components (Table 3.7, entries 1 and 2) although somewhat long reaction times were required. Slight activation of the aromatic aldehyde with electron withdrawing groups (entry 1) rather than electron donating groups (entry 2) increased product yields.

Ene reactions of 2-trimethylsilyloxypropene provided products in good to excellent yields with excellent enantioselectivity (entries 3-5) without any evidence of silyl transfer to the products. The scope of this reaction was broadened to include not only aromatic aldehydes (entry 3), but also aliphatic aldehydes (entries 4 and 5). Furthermore, Jacobsen demonstrated that this reaction could be carried out without solvent (entries 4 and 5). The use of chiral chromium complexes as catalysts in the carbonyl-ene reaction of enol ethers offers an alternative to Carreira's method and in contrast can produce excellent enantioselectivities with aromatic aldehydes.

Enantioselective studies of exocyclic enol ethers with chiral catalysts has been restricted to research done by Miles⁴⁶ and the Totah research group.⁴⁷ Miles demonstrated the

Table 3.7: *Jacobsen Carbonyl-Ene Reactions of Enol Ethers*

Entry	Enol Ether	Enophile	Solvent	time	catalyst	Yield (%)	% ee
1			acetone	36 h	509	88%	70
2			ethyl acetate	40 h	509	26%	89
3			acetone	40 h	509	75%	94
4			neat	72 h	510	83%	90
5			neat	20 h	510	90%	93

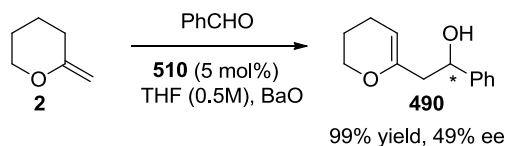
nucleophilic nature of 2-methylenedihydrofuran **474** in ene reactions with aldehydes. By utilizing chiral titanium BINOL catalyst, non-racemic mixtures of ene adducts resulted. Use of decanal **477** produced furan **511** in moderate yield with excellent enantioselectivity (Table 3.8, entry 1). Contrarily, benzaldehyde **479** provided furan **512** in excellent yield with only moderate selectivity (entry 2). Although these systems are driven by aromatization, this study substantiates that exocyclic enol ethers can deliver enantioselective products through chiral catalysis.

Table 3.8: Asymmetric Carbonyl-Ene Reactions of 2-Methylene-2,5-dihydrofuran

Entry	Substrate	Conditions	Product	Yield (%)	% ee
1		Et ₂ O, Ti(IV)/(S)-BINOL		65	94
2		Et ₂ O, Ti(IV)/(S)-BINOL		91	54

The Totah group has demonstrated degrees of stereoselective β-hydroxydihydropyran formation through chiral catalysis of the carbonyl-ene reaction of 2-methylenetetrahydropyrans. Catalyst **510**, previously discovered by Jacobsen to induce asymmetry in carbonyl-ene products of enol ethers,³⁵ was used to catalyze the reaction between exocyclic enol ether **2** and benzaldehyde (Scheme 3.18). This reaction provided β-hydroxydihydropyran **490** in near quantitative yield with moderate enantioselectivity. The barium oxide additive acted as a desiccant in the reaction.³⁵ The drawback of this reaction with 2-methylenetetrahydropyran is that determining the enantiomeric excess of the resultant products proved challenging. Decomposition of ene adducts resulted on HPLC chiral columns, and conversion to the Mosher ester caused elimination of the chiral center. These difficulties in judging stereoselectivity lead to another approach.

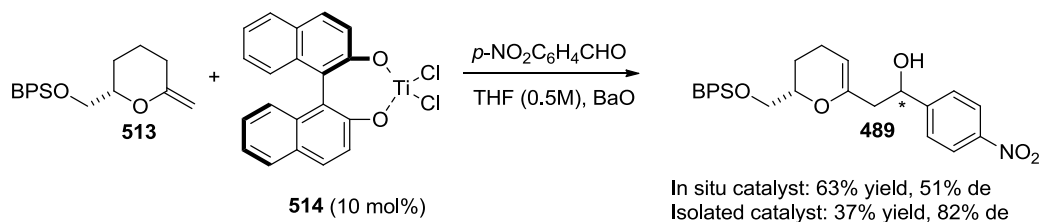
Scheme 3.18



Alternatively, C₆-substituted 2-methylenetetrahydropyran **513** was examined in the asymmetric carbonyl-ene reaction. This substrate was chosen so that the stereoselectivity of the

reaction could be judged through ^1H NMR integrations of diastereomeric products. The carbonyl-ene reaction of exocyclic enol ether **513** with titanium(IV) BINOL catalyst **514** and *p*-nitrobenzaldehyde **383** produced the desired dihydropyran **515**, but with yields and selectivities based on catalyst preparation (Scheme 3.19). *In situ* generation of the catalyst led to a moderate

Scheme 3.19



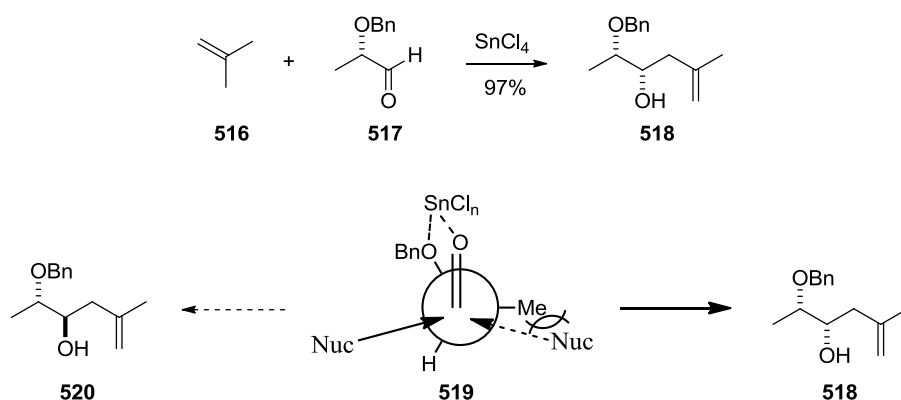
yield of product **515** with modest selectivity. Isolation of the catalyst prior to the reaction caused lower yields, but good diastereoselectivity was achieved. Although the C_6 -stereocenter could plausibly contribute to the observed selectivity, it is the chiral catalyst that is believed to induce generation of this new chiral center. The study of 2-methylenetetrahydropyrans bearing C_6 -stereocenters, which will be discussed later in this work, argues that chiral induction derived from the C_6 site is minimal.

Although the Totah group had moderate success at stereoselectively synthesizing 2-methylenetetrahydropyran ene adducts, that work concentrated on enantioselective processes utilizing chiral catalysis. The aim of this research is to determine the level of diastereoselective induction from substrate to product. Diastereofacial selection involves the preferential creation of a stereogenic center relative to a preexisting chiral center. Previous work in the field has demonstrated chiral induction to occur from both chiral enophiles and chiral enes. Although both types of research will be discussed, the latter is the focus of this paper.

Stereinduction from Enophile Components of the Carbonyl-Ene Reaction

Ene reactions that derive diastereoselectivity from chiral aldehydes primarily involve chelation of alpha or beta heteroatom-substituted aldehydes⁴⁸ and stereinduction through glyoxylate chiral auxiliaries.^{49,50,51} α -Oxygenated chiral aldehydes govern stereoselective product formation in the carbonyl-ene reaction based upon chelation control and Cram chelation models. This trend was first reported by Mikami through use of aldehyde **517** (Scheme 3.20).^{48a,48b}

Scheme 3.20

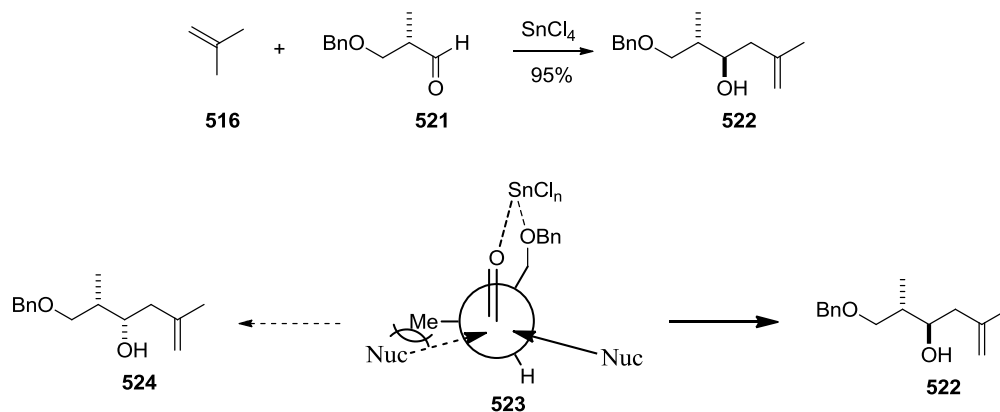


The ene reaction of 2-methylpropene **516** with alkoxy-aldehyde **517**, in the presence of tin(IV) chloride, resulted solely in the formation of ene adduct **518**. The presence of the α -alkoxy substituent on the enophile allows for chelation between it and the carbonyl with the Lewis acid. The preferred approach of the incoming olefin from the less hindered *si* face of this complex is presumably the basis for the observed stereoselectivity. Syn diol **518** resulted as the sole product.

Within the same work, Mikami also demonstrated diastereoselective preference for product **522** through use of chiral aldehyde **521** (Scheme 3.21). As discussed above, transition

state structure **523** predominated through cram chelation of enophile **521**. Nucleophilic attack from the less hindered *re* face results in production of ene adduct **522** in excellent yield. Thus

Scheme 3.21



the work of Mikami demonstrated that both alpha and beta-alkoxy aldehydes can diastereoselectively control formation of the new stereocenter formed in the carbonyl-ene reaction.

The diastereoselective production of ene adducts stemming from chiral α -amino aldehydes is dependant upon both the type of Lewis acid and choice of amino protecting group. The use of bidentate Lewis acids like Tin(IV) chloride (Table 3.9, entry 1) and titanium(IV) chloride (entry 4) provided the syn products through the cram chelation model as discussed above.^{48a} Substitution of N-Boc protecting groups for benzyl caused a decrease in yield along with an increase in diastereoselectivity (entry 2). More pertinent to our current study, silyl enol ether **531** also provided reasonable yields of the syn product under Tin(IV) chloride catalysis (entry 3). Thus, in the case of these bidentate Lewis acids, the alteration of either ene or enophile did not change the observed stereoselectivity.

Mikami discovered that use of monodentate Lewis acids like EtAlCl₂ in this reaction provided both syn and anti ene adducts based on the enophile's protecting group. α -

Dibenzylaminoaldehyde **525** resulted in production of syn product **532** (entry 5), while chiral N-Boc-aminoaldehyde **527** produced the anti ene adduct **533** (entry 6). The stereoselectivity of these reactions is best explained in terms of the Curtin-Hammett principal.⁵² The predominantly monodentate Lewis acids like EtAlCl₂ prefer to react through the non-chelation complex **535** (Scheme 3.22). This intermediate is much less reactive towards the ene reaction, however, than chelation complex **534**. When benzyl protecting groups are present on the enophile, the reaction proceeds through the chelation complex because the potential energy of

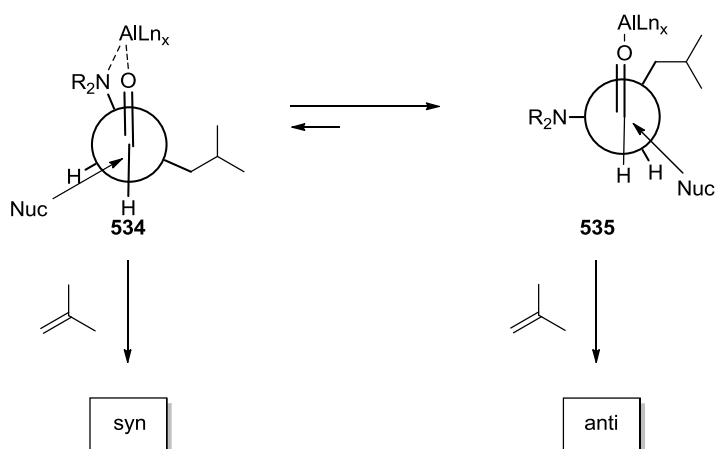
Table 3.9: Carbonyl-Ene Reactions of α -Aminoaldehydes

Entry	Ene	Enophile	Lewis Acid	Major Product	Ratio (syn:anti)	Yield
1			SnCl ₄		59%	73:27
2			SnCl ₄		41%	99:1
3			SnCl ₄		60%	91:9
4			TiCl ₄		25%	62:38
5			EtAlCl ₂		71%	99:1
6			EtAlCl ₂		40%	34:66

the system is too low to react through complex **535**. The syn products preferentially form in these cases (entry 5). Substitution of enophile **527** for **525** provides anti products, presumably due to the higher reactivity of N-BOC amino aldehyde **527**. The dependence of diastereoselectivity on the protective groups used demonstrates the sensitivity of these systems to changes in substrate.

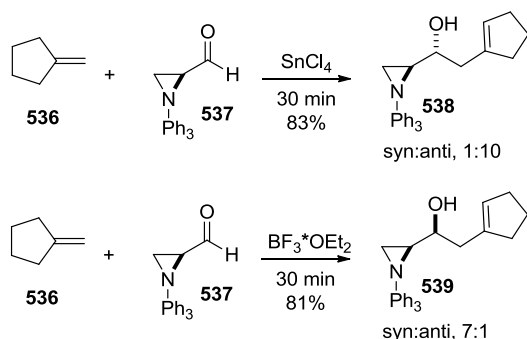
In a similar study of N-trityl aziridine-2-(S)-carboxaldehyde **537**, anti ene adducts predominated with use of Lewis acids capable of bidentate chelation, versus the syn products, which resulted from the use of monodentate Lewis acids.⁵³ The reaction of olefin **536** with

Scheme 3.22



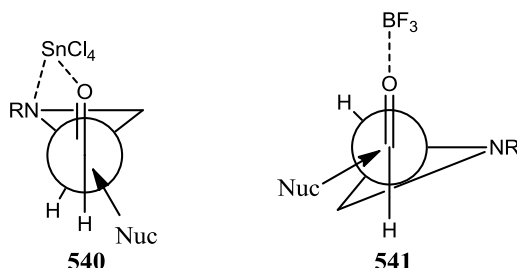
aldehyde **537** produced ene adduct **538** in good yield, favoring the anti diastereomer (Scheme 3.23). Bidentate chelation of the aldehyde to tin(IV) chloride results in complex **540** where

Scheme 3.23



nucleophile addition is favored from the less hindered *re* face (Figure 3.4). The large size of the N-trityl group blocks attack of the nucleophile from the *si* face. Alternatively, use of

Figure 3.4

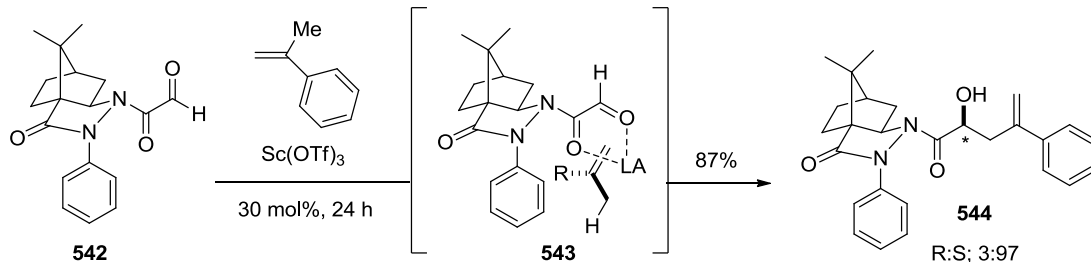


monodentate Lewis acid borontrifluoride etherate predominately produced the syn product **539**. This reaction proceeds through complex **541** according to the Felkin-Ahn model. This research corroborates that research done by Mikami,^{Error! Bookmark not defined.} which demonstrated how diastereoselectivity depended on substrates and Lewis acids used.

The ene reactions of glyoxylates bearing chiral auxiliaries are alternative types of diastereoselective processes that involves chiral aldehydes. These examples benefit in that the auxiliary can be added and removed, making these reactions applicable to many different types of glyoxylate-ene syntheses. Camphorpyrazolidinone⁴⁹ and 8-phenylmenthol^{50,51} have both been used as chiral auxiliaries for glyoxylate-ene reactions. Chen et al. discovered that N-glyoxyloyl camphorpyrazolidinone **542** effectively produced glyoxylate-ene adducts with moderate to high yields in the presence of Lewis acid catalyst scandium triflate.⁴⁹ Olefin 2-phenylpropene was found to achieve the best yield and diastereoselectivity for this reaction because of the pi overlap between the phenyl groups on both the enophile and incoming ene component (Scheme 3.24).

This reaction provided ene adduct **544** as the major isomer. The observed diastereoselectivity arises from preferred transition state **543**. The glyoxylate portion of enophile **542** complexes to the bidentate scandium trifoliate Lewis acid. This glyoxylate portion aligns

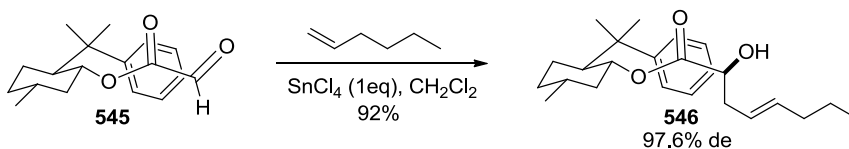
Scheme 3.24



parallel to the plane of the N-benzyl ring to optimize stabilizing pi orbital overlap between the two groups. The olefin component attacks from the less sterically hindered back face of this complex to provide product **544**. Although this reaction provided the best yields and diastereoselectivity, the authors demonstrated a range of 2-substituted propenes to work in this study.

In a similar reaction, glyoxylate **545** produced ene adduct **546** when combined with 1-hexene in the presence of equimolar amounts of tin(IV) chloride (Scheme 3.25).⁵⁰ Unlike the camphor derived auxiliary, glyoxylate **545** is not locked into a rigid structure. Nonetheless the chair conformation shown is highly favored from an all-equatorial arrangement of substituents. The glyoxylate portion of the structure aligns with the phenyl pi electron cloud to optimize stabilizing pi orbital overlap. Attack of 1-hexene from the front, *si* face, which is not blocked by the aromatic ring, then affords alcohol **546** as the predominant isomer.

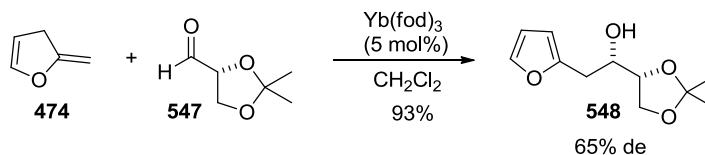
Scheme 3.25



Examples of chiral induction derived from stereogenic aldehydes and their application to exocyclic enol ethers are scarce. Miles demonstrated that β -hydroxyfuran **548** could be produced in excellent yield with moderate diastereoselectivity from chiral aldehyde **547** (Scheme

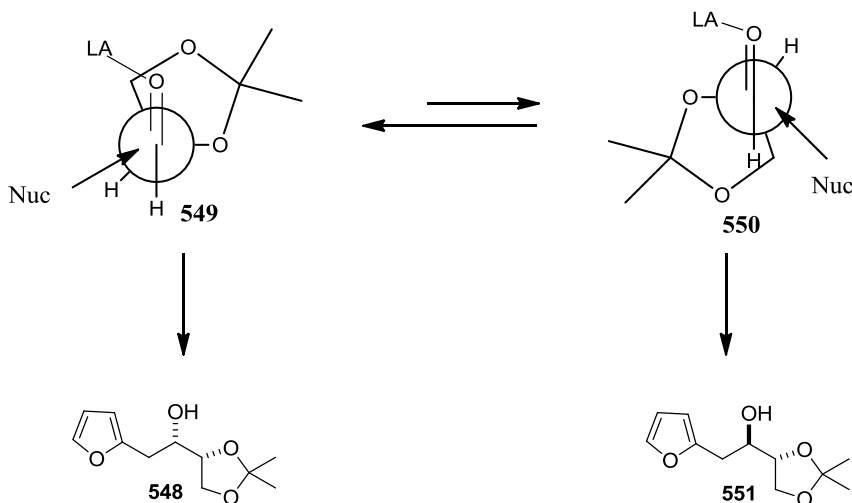
3.26).⁴⁶ The observed diastereoselectivity is derived from Felkin-Ahn model **549** (Scheme 3.27). Conformer **549** is preferred over conformation **550** due to minimization of torsional strain

Scheme 3.26



Attack of the incoming nucleophile occurs from the most accessible *si* face, resulting in major diastereomer **548**.

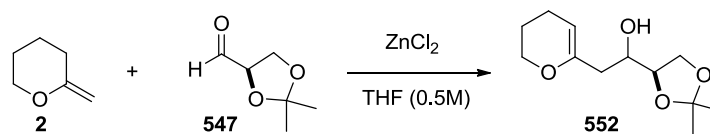
Scheme 3.27



The Totah research group also demonstrated chiral aldehyde **548** to induce diastereoselectivity in β -hydroxydihydropyran products (Table 3.10).⁴⁷ Chiral aldehyde **547** was combined with 2-methylenetetrahydropyran **2** to produce carbonyl-ene adduct **552** as a mixture of diastereomers. The best yields were obtained after 24 hours (entry 2), and the products were obtained as a modest 2.4:1 ratio of diastereomers. The identity of the major diastereomer could not be identified through Mosher ester modification because of the propensity of these systems toward elimination. Both shorter (entry 1) and longer (entry 2) reaction times resulted in decreased

product yields, but had little to no effect on stereoinduction. Increasing catalyst loading caused reduction in yields and little effect on diastereoselectivity (entry 4).

*Table 3.10: Carbonyl-Ene Reactions of Exocyclic Enol Ether **2** with Chiral aldehyde **547***



Entry	Mol % ZnCl_2	Time	Yield	dr
1	5	8	59%	2.3:1
2	5	24	98%	2.4:1
3	5	30	64%	2.5:1
4	20	24	82%	2.3:1

Stereoinduction and Transfer from Ene Components of the Carbonyl-Ene Reaction

The olefin component of the ene reaction has been shown to demonstrate chiral induction in resulting products. Types of influences derived from chiral ene constituents include those from substituted olefins, olefins possessing allyl hydroxyl groups, and ene components that contain large facial preferences. Choice of Lewis acid with enes possessing E or Z olefin geometry will influence the stereochemical outcome of products. Subjection of (*E*) and (*Z*)-2-butenes produced both erythro and threo products depending on the type of Lewis acid employed.^{48a,54} Use of equimolar quantities of bidentate tin(IV) chloride preferentially produced threo product **553** (Table 3.11, entries 1 and 2). The observed stereochemistry is based from chair transition states **555** and **556** (Figure 3.5). Chair transition states **555** and **556** correspond toward the manufacture of threo product **553**. The bidentate metal promoter binds to both carbonyls of the glyoxylate enophile. Both models minimize unfavorable steric interactions between the olefin methyl group and the relatively large Lewis acid metal as opposed to transition state **557** which gives rise to erythro isomer **554**.

Table 3.11: Carbonyl-Ene Reactions of (*E*) and (*Z*)-2-Butenes

Entry	Ene Geometry	Lewis Acid	Yield	Major Product	Erythro:Threo
1	<i>E</i>	SnCl ₄	100%		18:82
2	<i>Z</i>	SnCl ₄	100%		28:72
3	<i>E</i>	Me ₂ AlOTf	29%		79:21
4	<i>Z</i>	Me ₂ AlOTf	65%		91:9

Figure 3.5

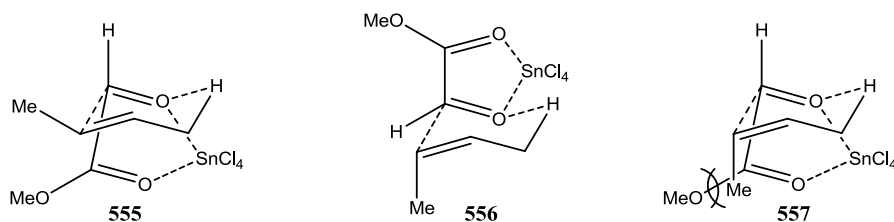
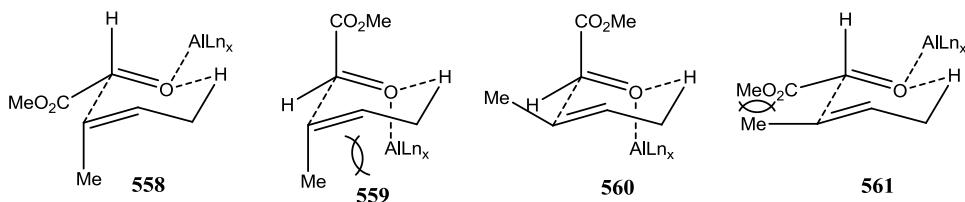


Figure 3.6 alternatively shows the chair transition states associated with manufacture of threo isomer **554** through use of monodentate aluminum Lewis acids. The aluminum Lewis acid complexes anti to the glyoxylate, and as a result transition state **558** predominates for the *Z*

Figure 3.6

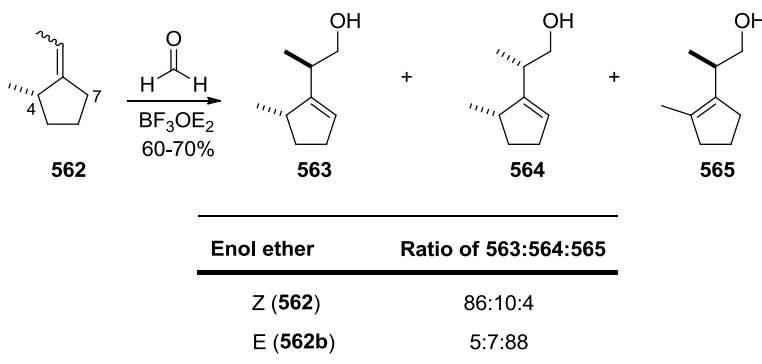


isomer to avoid steric repulsion between the pendant methyl group and bulky Lewis acid. Similarly, (*E*)-2-butene proceeds through transition state **560** as opposed to model **561**, which experiences steric repulsion between these two groups. In conclusion, this research demonstrates

how bidentate and monodentate Lewis acids demonstrate preference toward erythro and threo isomers respectively with E and Z olefins based on steric repulsions in their respective transition states.

The research of Wovkulich⁵⁵ demonstrates how chiral, tri-substituted olefins transpose selectivity onto corresponding products through a combination of steric effects. The ene reaction of enol ethers **562** and **562b** (Z and E isomers) with formaldehyde resulted in production of alcohol isomers **563**, **564**, and **565** with ratios 86:10:4 and 5:7:88 respectively (Scheme 3.28). While the reaction of Z olefin **562** occurred regio and stereoselectively, primarily creating isomer **563**, the reaction of E olefin **562b** predominantly produced regioisomer **565**.

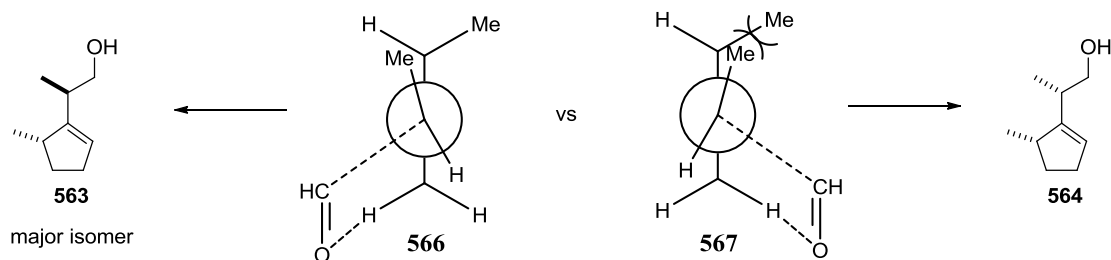
Scheme 3.28



The high relative stereoselectivity associated with the E olefin results through the unification of two steric models where effects originate from both the olefinic and cyclic methyl groups. Firstly, the aldehyde-Lewis acid complex is favored to attack from the β face, opposite the cyclic methyl group due to steric interactions, which would preferentially lead to isomer **563** production. Secondly, the aldehyde complex prefers to attack the β face of the ring based on steric interactions that arise between the olefinic and cyclic methyl groups (Scheme 3.29). As the formaldehyde complex attacks the olefin, the olefinic carbon is bent out of plane with the ring. This forces a steric interaction between the olefinic methyl and the cyclopentyl ring.

Transition state **566** predominates, because methyl-methyl non-bonding interactions are minimized as compared to transition state **567**. In effect ene adduct **563** is produced and the cumulative combination of both types of steric influence gives rise to the good selectivity observed for this reaction.

Scheme 3.29

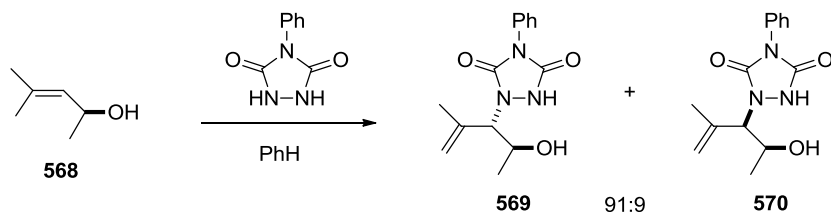


The reaction of E isomer **562b**, on the other hand, results in minor selectivity between isomers **563** and **564**. In fact, isomer **565** was primarily produced since the C₄ hydrogen is more sterically accessible towards abstraction than the C₇ hydrogens. The only source of stereochemical preference in this reaction is the favored addition of the formaldehyde complex from the face opposite the cyclic methyl group. The E isomer does not experience methyl-methyl interactions as the enophile enters, thus lowering the effective stereoselectivity of this system as compared to the Z isomer. Nonetheless these examples demonstrate the strong directing capabilities of chiral ene substrates toward their products.

The ene reaction of chiral allylic alcohols with singlet oxygen,⁵⁶ triazolinediones,⁵⁷ and *p*-nitronitrosobenzene⁵⁸ leads predominantly to threo ene adducts due to hydroxyl steering effects. For example, chiral alcohol **568** yielded products **569** and **570** as a 91:9 ratio of diastereomers when subjected to phenyltriazolinedione (Scheme 3.30). The *pi* facial selectivity of this reaction and that of singlet oxygen is derived from the pendant alcohol, which is shown in

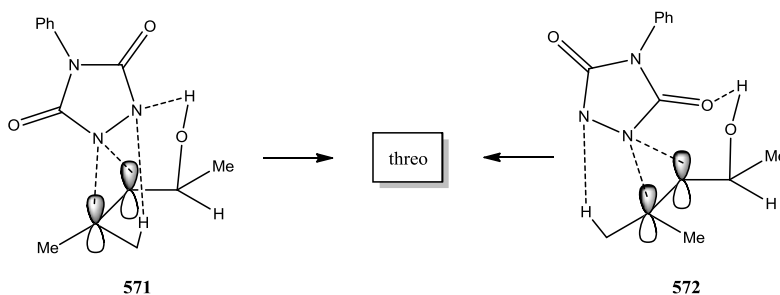
transition state models **571** and **572** (Scheme 3.31). Masking of the hydroxyl or replacement of the alcohol moiety by an alkyl group results in significantly lower stereoselectivity.

Scheme 3.30



1,3-Allylic strain plays a role in the stability of the transition states. The chiral methyl group adopts an orientation that minimizes non-bonding interactions with the syn allylic methyl group. The incoming enophile is then directed through hydrogen bonding with the alcohol. Abstraction of the syn-hydrogen (transition state **571**) is slightly favored over the anti-hydrogen (transition state **572**), but nonetheless both models result in formation of the threo product. Choice of solvent affects these systems in that nonpolar solvents like dichloromethane and benzene deliver great threo selectivity, while polar solvents like acetone and methanol produce poor diastereoselectivity. The production of erythro products in these cases accompanies the threo product, because directive hydrogen bonding is blocked by solvent interactions.

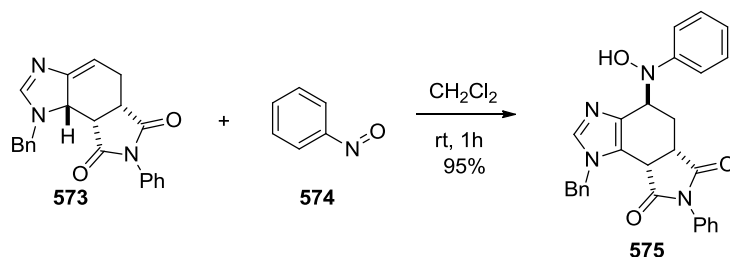
Scheme 3.31



Olefins which possess a face with considerable steric bulk have demonstrated chiral induction in the carbonyl-ene reaction, affecting the stereochemistry of the alkoxy carbon formed. The ene reaction of ring system **573** with aryl nitroso compounds produced aromatic

ene adducts as single diastereomers (Scheme 3.32).⁵⁹ In these examples no Lewis acid catalyzation is required due the aromatization driving force. The steric influence is based entirely on the structure of the nucleophilic ene component, where addition of the enophile

Scheme 3.32



comes from the top face. The three-ringed system of olefin **573** possesses a convex and concave face where the top, convex face has less steric interference with the incoming enophile thus leading to structure **575**.

β -Pinene derived enes **576** have produced carbonyl-ene products with considerable selectivity about the new hydroxyl center.^{60,61} Use of a ruthenium salen catalyst produced alcohols **577** as a mixture of isomers in a 81:19 ratio (Scheme 3.33). The isomers were not assigned to the ratios obtained, however, approach of the aldehyde theoretically occurs from

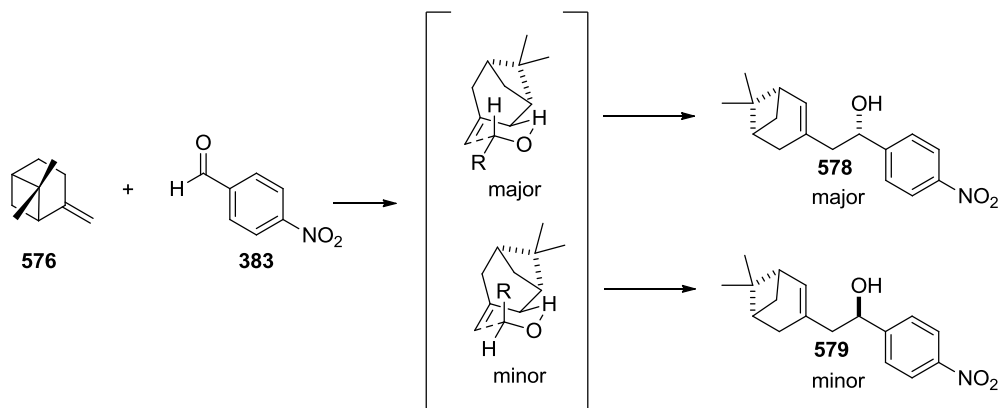
Scheme 3.33



opposite the bridged system. A chair transition state results, where the aldehyde approaches such that the aromatic ring is held equatorial to avoid steric strain (Scheme 3.34). From this transition state alcohol **578** is predicted to predominate over isomer **579**. This stereochemical model is purely steric based on the ene substrate and not the ruthenium catalyst used. Reactions of olefins

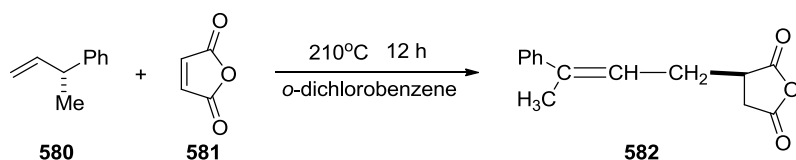
possessing sterically equivalent faces with the same catalyst did not result in selective product formation.

Scheme 3.34



Chirality transfer from ene components has been studied both in thermal and Lewis acid catalyzed systems. Chirality transfer occurs through destruction of the original stereocenter with concomitant creation of a new one. Study of this subject pertaining to the thermal ene reaction demonstrated that stereoselectivity was based entirely on steric considerations. The thermal reaction of (*R*)-3-phenyl-1-butene **580** with maleic anhydride **581** produced ene adduct **582** as the major isomer (Scheme 3.35).⁶² Either exo or endo transition states (Figure 3.7) lead to

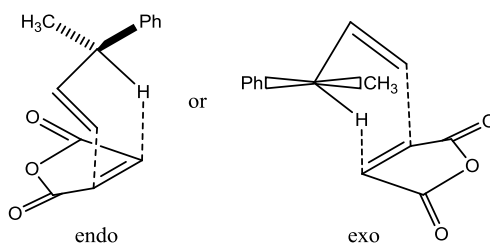
Scheme 3.35



production of the *R* enantiomer. The observed selectivity is based on the steric argument that the larger phenyl group orients away from the maleic anhydride as the two molecules approach.

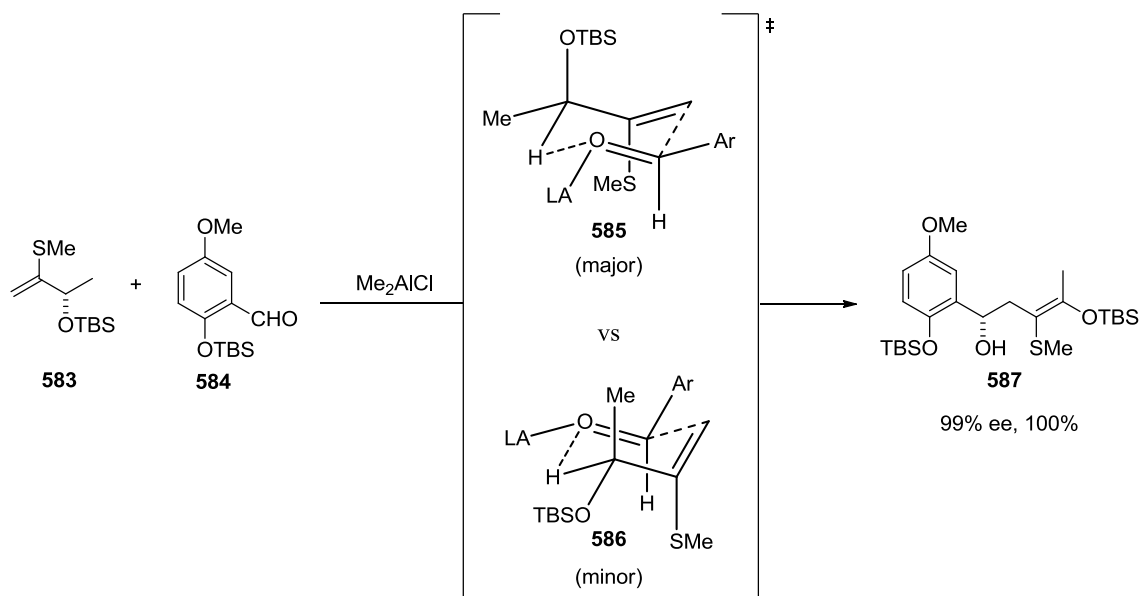
Chirality transfer in Lewis acid catalyzed systems has produced products with good selectivity. Kuwajima demonstrated that allylic silyl ether **583** formed ene product **587** asymmetrically (Scheme 3.36).^{43b} The reaction proceeds through a chair transition state where

Figure 3.7



the large Lewis acid avoids steric interactions by chelating anti to the aromatic group on the aldehyde. An equatorial orientation of the Lewis acid and phenyl group as the two molecules come into proximity avoids unwanted 1,3-diaxial interactions with the ene substituents. Furthermore the reaction proceeds through transition state **585** opposed to **586** to avoid the steric interactions of the ene methyl substituent.

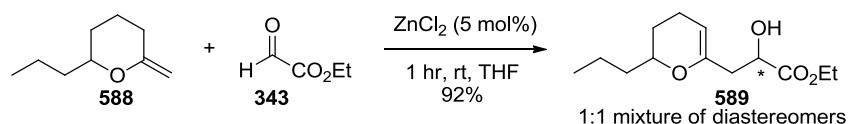
Scheme 3.36



The intermolecular carbonyl-ene reactions discussed have demonstrated high levels of stereoselectivity through chiral catalysis and stereo induction or transfer from both enophile and ene components. Chirality induction from ene components has shown to be somewhat substrate dependent. Chirality induction studies of exocyclic enol ethers have only been evaluated with

octanolactone-derived enol ether **588** in the Totah research group (Scheme 3.37). The study of enol ether **588** with ethyl glyoxylate **343** resulted in a 1:1 diastereomeric mixture of products at the alcohol center, which indicates little to no chiral induction from the C₆ stereocenter in the starting enol ether. Therefore the objective is to explore the influence of stereocenters at other positions about the tetrahydropyran ring of exocyclic enol ethers.

Scheme 3.37

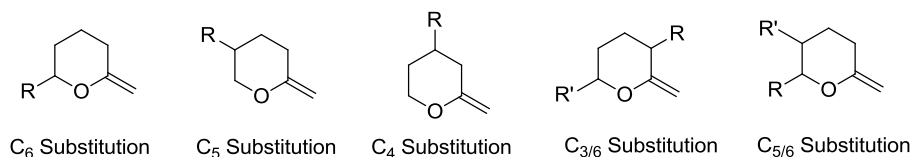


3.3 Results and Discussion

As described, the non-stereoselective carbonyl-ene reaction of 2-methylenetetrahydropyrans has been studied to provide the corresponding ene adducts in good yield with aldehydes that range in reactivity. Addition of functionality to the tetrahydropyran ring is anticipated to impact the stereoselectivity of this reaction through influence of the ring conformation. The presence of ring substituents would also create new steric interactions with the incoming enophile, resulting in proximity effects that influence product stereochemistry.

The goal of this research is to explore how substituted 2-methylenetetrahydropyrans could induce stereoselectivity into the resulting carbonyl-ene products. To reach this end, we sought to study exocyclic enol ethers that contained one or more stereocenters at positions 3, 4, 5, and 6 about the ring (Figure 3.8). Although the implication for this research is the asymmetric

Figure 3.8

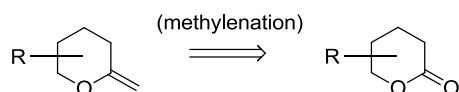


preparation of functionalized tetrahydropyrans, the substrates are prepared as racemic mixtures. This allows for measure of the carbonyl-ene reaction's diastereoselectivity through ^1H NMR integration of the resulting products.

Synthesis of 2-Methylenetetrahydropyrans

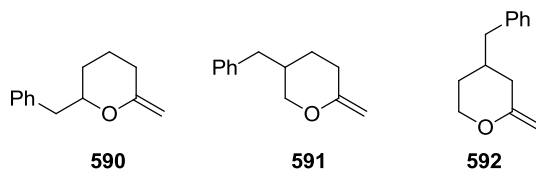
Initial work was aimed toward the stereoselective synthesis of enol ethers for use in the diastereoselective carbonyl-ene study of 2-methylenetetrahydropyrans. These substrates were generally synthesized through conversion of the corresponding lactone via methylenation (Scheme 3.38).

Scheme 3.38



Initial studies focused on the preparation of exocyclic enol ethers containing a single substituent about the ring. These enol ethers were synthesized so the extent of chiral induction of one pendant group in relation to its proximity to the site of proton abstraction could be examined. The exocyclic enol ethers prepared contained a benzyl substituent at the C₆ (**590**), C₅ (**591**), or C₄ (**592**) position on the 2-methylenetetrahydropyranyl ring (Figure 3.9).

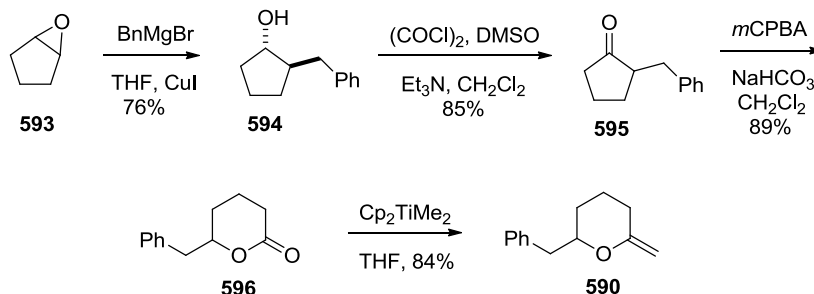
Figure 3.9



Although chiral induction has been studied from C₆ substituents on octanolactone derived enol ethers to the corresponding carbonyl-ene products, enol ether **590** was synthesized to confirm the lack of diastereoselective product formation. This enol ether was prepared in 4 linear steps (48%) from cyclopentane oxide **593** (Scheme 3.39). Copper catalyzed ring opening

of cyclopentane oxide **593** with benzyl Grignard gave alcohol **594** as a single diastereomer. Swern oxidation⁶³ of the resulting secondary alcohol led to ketone **595**, which was readily converted to lactone **596** via Baeyer-Villiger oxidation.⁶⁴ Subsequently, lactone **596** yielded desired enol ether **590** in 84% yield upon treatment with Petasis reagent.⁶⁵

Scheme 3.39

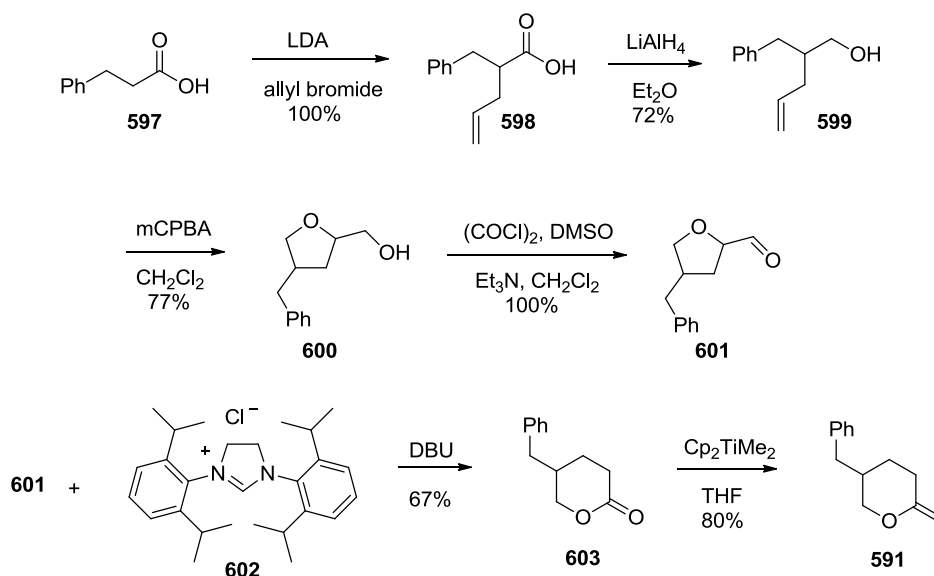


Synthesis of enol ethers **591** and **592** was achieved according to the method developed by Gravel.⁶⁶ Oxacycloalkane-2-carboxaldehydes were converted to the corresponding lactones by N-heterocyclic carbene catalyzed ring-expansion/lactonization. Enol ether **591** was synthesized from hydrocinnamic acid **597** in 6 linear steps (30% overall yield) via the route outlined by Gravel (Scheme 3.40).⁶⁶ In this sequence, direct alkylation of hydrocinnamic acid **597** with allyl bromide afforded carboxylic acid **598**. Reduction of the carboxylic acid **598** with LiAlH_4 afforded alcohol **599** in 72% yield as opposed to the 10% reported for this transformation.⁶⁶ Tetrahydrofuran **600** was then prepared from alkene **599** upon epoxidation with $m\text{CPBA}$ and subsequent epoxide opening under acid catalyzed conditions. A mixture of diastereomers was obtained (1:1.3) from this reaction, however loss of the α -hydroxy chiral center in a subsequent step makes this poor selectivity of little concern.

From here aldehyde **601** was obtained by Swern oxidation of the primary alcohol. Though in the original report⁶⁶ this transformation was achieved with IBX oxidation, we found Swern conditions to be superior (100% yield with Swern as compared to the reported 84% yield

with IBX). Lactone **603** was formed after N-heterocyclic carbene (NHC)-catalyzed ring expansion-lactonization of aldehyde **601**. The proposed mechanism of this reaction is outlined in Scheme 3.41.

Scheme 3.40

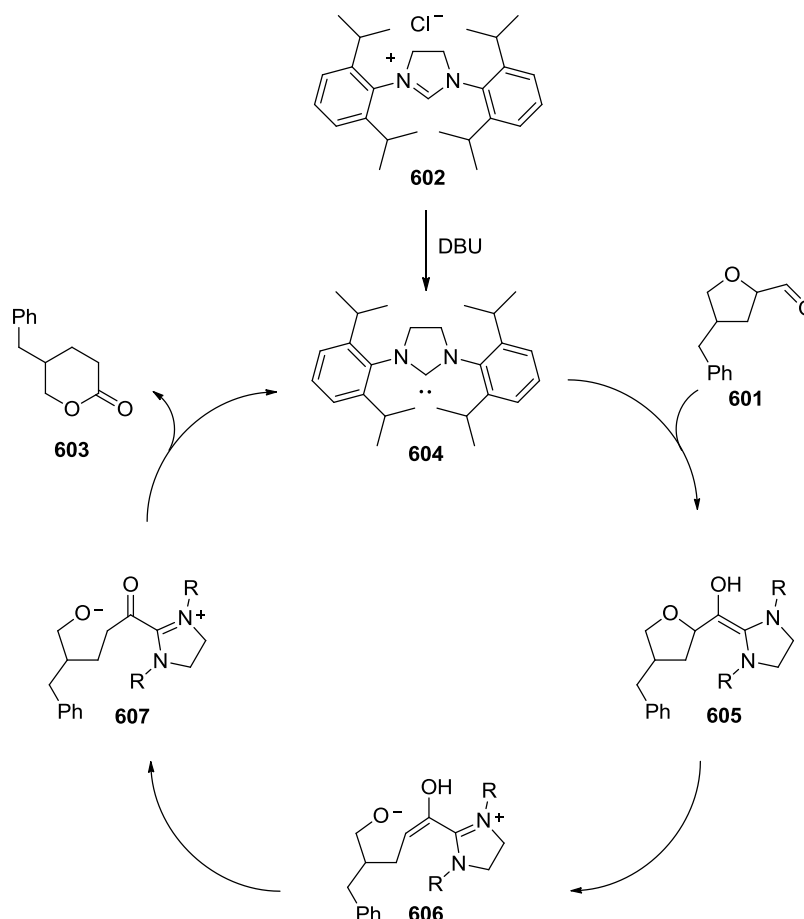


NHC **604** was produced from DBU deprotonation of heterocycle **602**. Combination of the newly formed NHC with 2-carboxaldehyde **601** delivered Breslow intermediate **605**, which was prepared for ring opening. Tautomerization of ring opened intermediate **606** led to ketone intermediate **607**, which upon intramolecular cyclization provided the desired lactone **603** and the regenerated NHC catalyst. Thereafter, Petasis olefination yielded desired enol ether **591** in 80% yield.

Enol ether **591** was synthesized over 8 linear steps, in 20% overall yield, from benzeneacetaldehyde **608** (Scheme 3.42). Horner-Wadsworth-Emmons reaction of benzeneacetaldehyde **608** gave predominantly *trans*-alkene **609**. Olefination was followed by DIBAL reduction to afford alcohol **610** in quantitative yield. Although this reaction was

performed following the procedure outlined in Gavel's publication, the obtained yield of alcohol **610** far surpassed the published yield of 76%.⁶⁶ Upon heating alcohol **610** in the presence of

Scheme 3.41

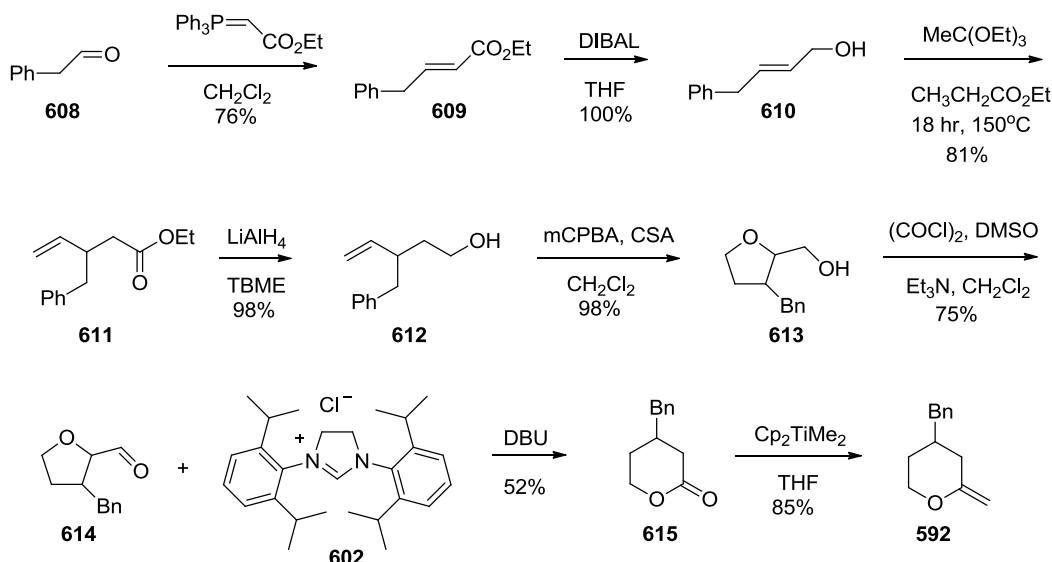


triethyl orthoacetate, a Johnson- Claisen rearrangement occurred giving ester **611** in 81% yield as opposed to the 70% published yield.⁶⁶ Subsequent lithium aluminum hydride reduction provided alcohol **612** in 98% yield. Again, the obtained yield for this reduction surpasses that reported (54%).⁶⁶

Treatment of the resulting alcohol **612** with *m*CPBA resulted in formation of tetrahydrofuran **613**, as previously discussed (cf. Scheme 3.40). The poor mixture of diastereomers obtained (1:1.4) was of little consequence since one stereocenter is destroyed in a

proceeding step. Oxidation of alcohol **613** provided aldehyde **614**. Here too, Swern oxidation was used rather than the reported⁶⁶ Dess-Martin Periodinane,⁶⁷ Subsequent N-heterocyclic

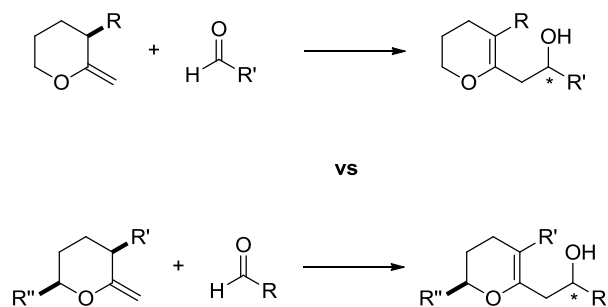
Scheme 3.42



carbene catalyzed ring expansion-lactonization led to lactone **615**. Finally, Petasis methylenation gave rise to desired enol ether **592** in 84% yield. In general, the routes described here for the synthesis of enol ethers **591** and **592** proved to be quite efficient, with many of the yields exceeding those reported.

Mono-substituted 2-methylenetetrahydropyrans bearing substitution at the C₃ carbon were not synthesized for this diastereoselective ene study. Application of this enol ether to the carbonyl-ene reaction would not provide diastereomer products, because the C₃ stereocenter is lost in the reaction (Scheme 3.43). This absence of diastereomers causes difficulty in determining the stereoselectivity of the reaction as previously demonstrated by the Totah research group.⁴⁷ Analysis of 2-methylenetetrahydropyran ene adducts by HPLC led to their decomposition on the chiral column. Addition of shift reagents in the ¹H NMR spectra produced poor results, such that the ratio of enantiomers could not be evaluated. Lastly, derivativization to

Scheme 3.43



the Mosher ester led to olefin byproducts due to the propensity of ene adducts to undergo elimination. These difficulties directed us toward the study of 2-methylenetetrahydropyrans with two substituents about the ring. The ene reaction of these substrates would provide the desired set of diastereomer products that could be analyzed by ^1H NMR analysis (Scheme 3.43). The C_6 stereocenter present on these systems was not expected to influence product selectivity as was previously established.⁶⁸

Not only were di-substituted 2-methylenetetrahydropyrans synthesized for evaluation of chirality transfer due to the C_3 center, but also for the study of axial versus equatorial effects of substituents. The substituents on the monosubstituted enol ethers **590**, **591**, and **592** are expected to adopt an equatorial configuration the majority of the time. By placing two stereogenic centers on the ring, two isomers of the same enol ether can be tested, one which has an all-equatorial conformation (**616**) and another where one substituent must be axial (**619**) (Scheme 3.44). Enol ethers **622/623** and **624/625** were manufactured to study these axial/equatorial substitution effects of the tetrahydropyran ring (Figure 3.10). The synthesis of these enol ethers allows for evaluation of C_6/C_5 and C_6/C_3 -substituted systems. The manufacture of a C_6/C_4 exocyclic enol ether system was attempted, however these efforts proved unsuccessful.

Scheme 3.44

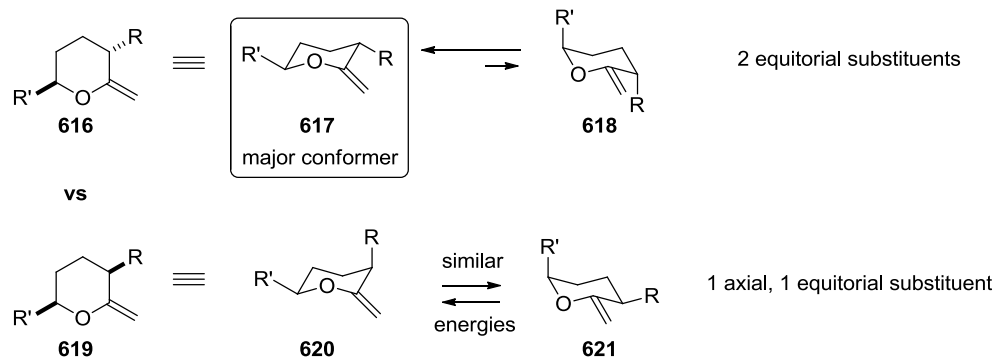
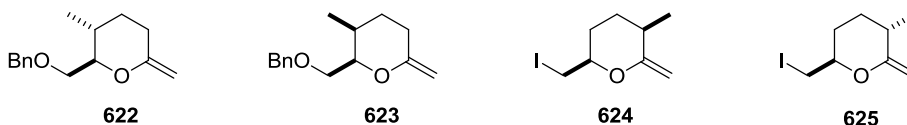
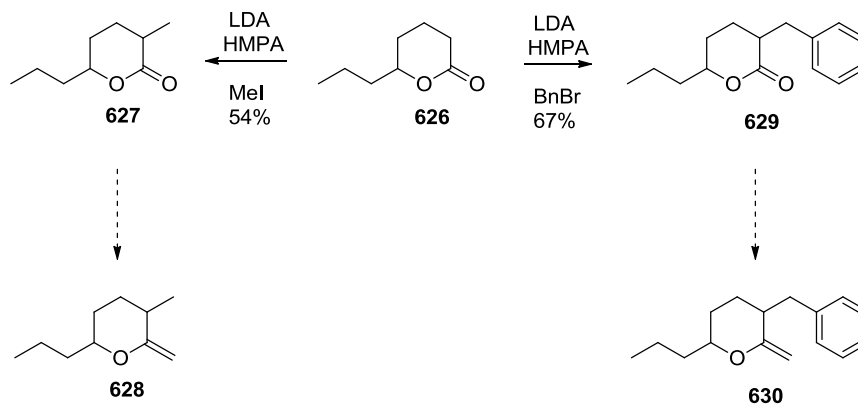


Figure 3.10



Initial studies toward the synthesis of di-substituted 2-methylenetetrahydropyrans, containing C₃ chiral centers, began with the synthesis of enol ether **628**. This enol ether was chosen, because it could be synthesized from commercially available octanolactone in two short synthetic steps (Scheme 3.45). Lactone **627** was synthesized as a 1:2 mixture of diastereomers

Scheme 3.45



through direct alkylation of commercially available octanolactone **626**. At this point, separation of the two lactone diastereomers was envisioned by column chromatography such that each could be converted into the corresponding enol ether and then individually studied in the

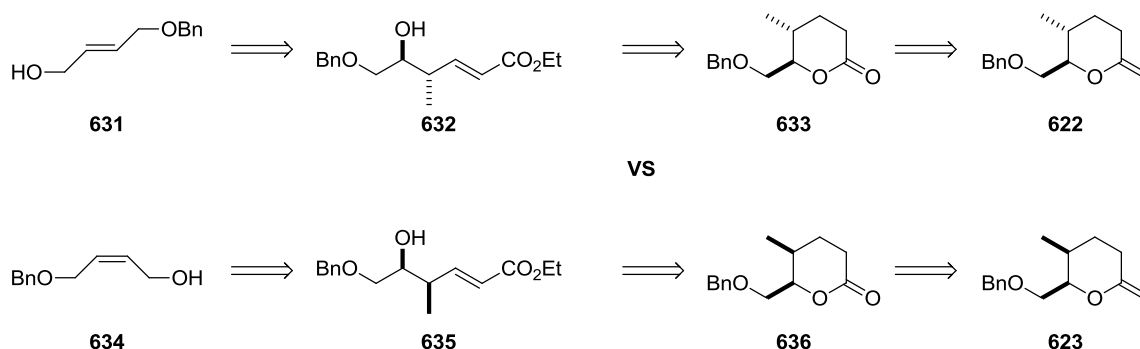
carbonyl-ene reaction. Separation of the individual diastereomers, however, proved unsuccessful by flash column chromatography.

Since separation of lactone **628** diastereomers could not be achieved by silica gel chromatography, the related benzyl substituted lactone **629** was synthesized to facilitate separation by HPLC equipped with a UV detector. Lactone **629** was again synthesized through alkylation of the commercially available octanolactone **626**. Unfortunately, here too, neither flash column chromatography nor HPLC proved successful for separation of the *cis* and *trans* diastereomers of compound **629**. Therefore other routes toward the synthesis of di-substituted enol ethers were investigated.

Enol ethers **622** and **623** were synthesized so that the effects axial substituents have on chiral induction can be evaluated in a C₆/C₅ substituted system. Enol ether **623** has two *cis*-related substituents at C₅ and C₆. Therefore, one of the substituents must lie in equatorial position while the other is axial (Scheme 3.44). Alternatively, in enol ether **622**, both substituents are equatorial.

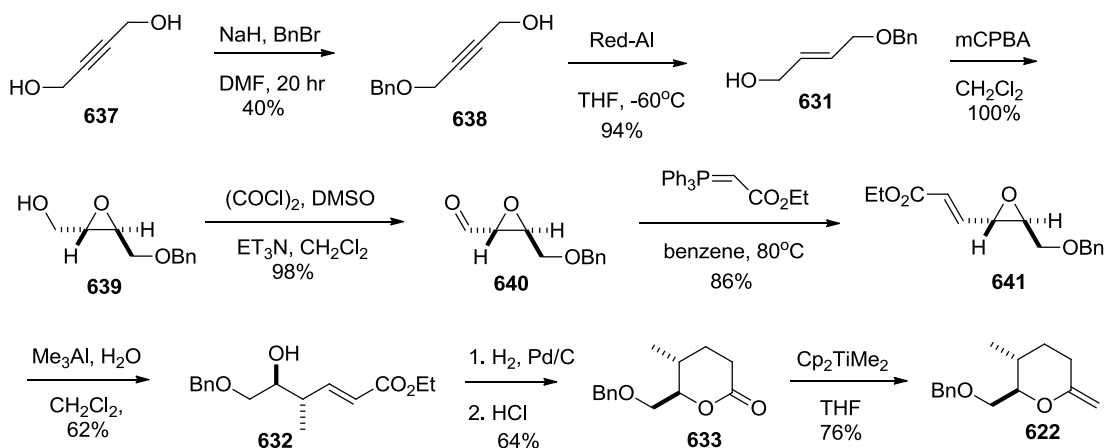
The synthesis of enol ethers **622** and **623** are similar, but differ in the geometry of the olefin intermediate. Compound **622** is derived from the *E*-olefin **631**, whereas compound **623** is derived from the *Z*-alkene **634** (Scheme 3.46). Formation of the *trans*-C₆/C₅ substituted

Scheme 3.46



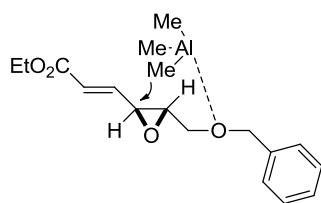
exocyclic enol ether **622** was accomplished, beginning with 2-butyne-1,4-diol **637** (Scheme 3.47). Diol **637** was monoprotected with benzyl bromide to form alcohol **71**,⁶⁹ which was

Scheme 3.47



selectively reduced to the *trans*-alkene **631** using Red-Al. Treatment with *m*CPBA then afforded epoxide **639** as a single diastereomer.⁷⁰ Alcohol **639** was subsequently oxidized to the corresponding aldehyde **640** under Swern conditions.⁷¹ Horner Wadsworth Emmons olefination of aldehyde **640**, using freshly prepared carbethoxymethylene triphenylphosphorane,⁷² led solely to the *trans*-epoxy-alkene **641**. Addition of trimethylaluminum and water to epoxide **641** regioselectively produced alcohol **632** as the only isomer.⁷³ The observed regioselective addition, of the methyl group to the epoxide, which proceeds through a six-membered transition state, is based on the coordination of the Lewis acid (Me₃Al) to the benzyl ether (Figure 3.11).

Figure 3.11

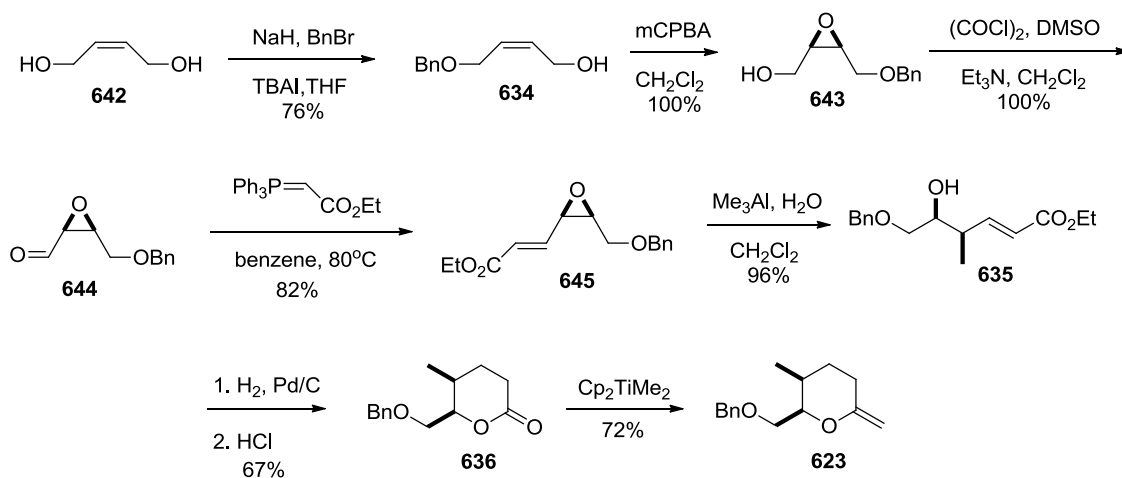


The next step in this sequence, hydrogenation of the double bond, proved difficult. Nonetheless, reduction of olefin **632** was accomplished, surprisingly, without removal of the

benzyl protecting group. The difficulty with this reaction occurred as the process was scaled up. The reaction only proceeded under vigorous stirring with larger proportions of Pd/C as the amount of substrate increased. In these cases Pd/C was added by increasing the mole percent by 0.2% every 24 h until the reaction was complete. Adding large amounts of Pd/C was avoided to circumvent concomitant benzyl removal. Reduction of the double bond resulted in partial cyclization of the ester to afford mixtures of lactone **633** and the corresponding ester (3:1-1:1 respectively). The mixture of compounds was washed with acid to complete the cyclization, yielding lactone **633**. Petasis olefination then provided desired *trans*-5,6-substituted exocyclic enol ether **622** in 76% yield.

The synthesis of enol ether **623** is outlined in Scheme 3.48. Monoprotection of 2-butene-1,4-diol **642** with benzyl bromide formed alcohol **634**.⁷⁴ Subjection of alcohol **634** to *m*CPBA resulted in production of epoxide **643** as a single diastereomer with yields exceeding that published.⁷⁰ The resulting alcohol was then oxidized under Swern conditions to aldehyde **644**.⁷⁵ Olefination and subsequent epoxide-opening with trimethyl aluminum led to alcohol **635**.⁷⁶

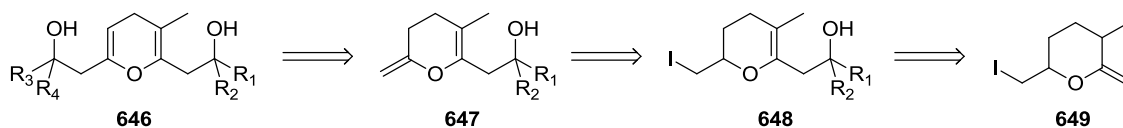
Scheme 3.48



Selective hydrogenation of substrate **635** again reduced the olefin without benzyl deprotection to form a mixture of lactone **636** and the ester (2:1-1:1 respectively). Subjection of this mixture of compounds to acidic conditions furnished lactone **636** in 67% yield (over two steps). Petasis olefination of lactone **636** then produced desired 2-methylenetetrahydropyran **623**.

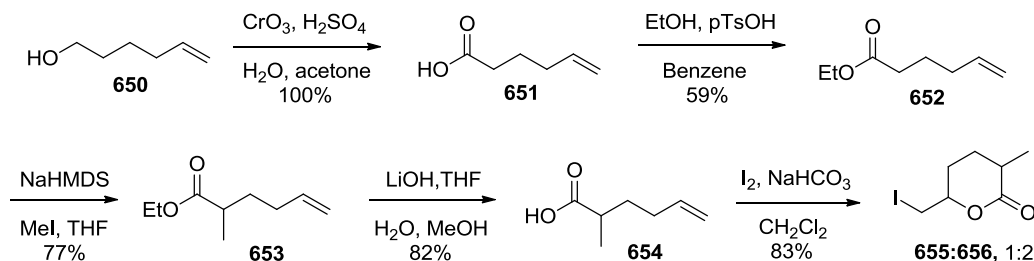
The last two substrates prepared were enol ethers **624** and **625**. Evaluation of these enol ethers in the ene reaction may help to determine the influence a C₃ substituent has on the selectivity observed in the carbonyl-ene reaction. These enol ethers contain a pendent C₆ iodomethyl substituent that could subsequently be eliminated to form a second enol ether. These enol ethers can not only be used in the chiral transfer study, but also used in bi-directional carbonyl-ene reactions (Scheme 3.49). The iodomethyl group was chosen as the C₆ substituent because diastereomeric mixtures of these lactones are known to be separable⁷⁷ as opposed to those that were previously attempted (Scheme 3.45)

Scheme 3.49



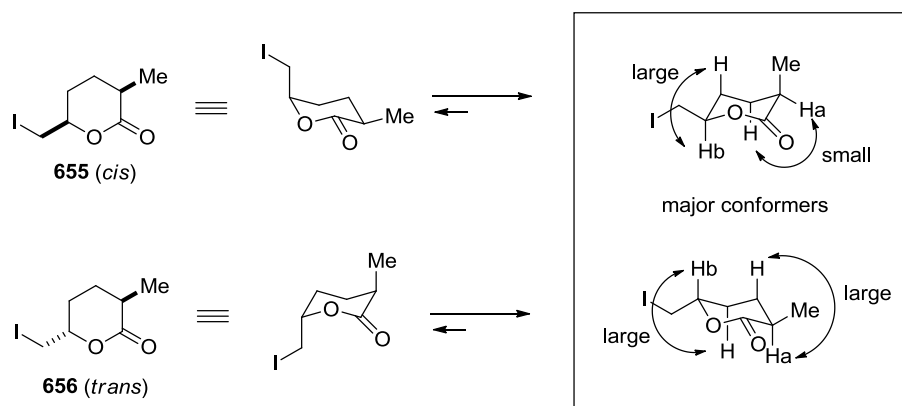
Lactones **655** and **656** were prepared as a mixture of diastereomers and subsequently separated via HPLC. Their synthesis is outlined in Scheme 3.50. Carboxylic acid **651** was synthesized in quantitative yield from 1-hexen-6-ol **650** via known Jones oxidation.⁷⁸

Scheme 3.50



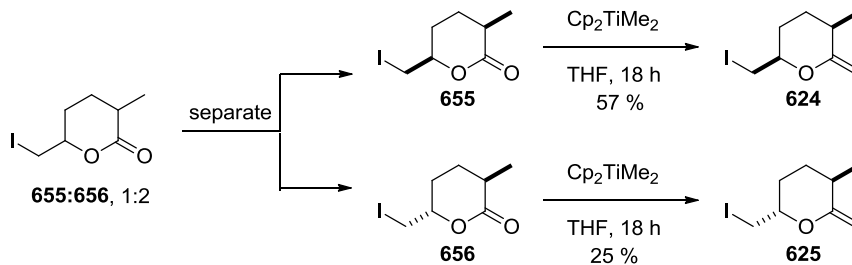
Esterification and subsequent methylation led to ester **653**.⁷⁹ Direct iodocyclization of this compound failed to produce the desired lactones, in contrast to previously published results of 5-carboxy-1-penten-3-ones.⁸⁰ Therefore hydrolysis of ester **653** was done to provide carboxylic acid **654**. Iodocyclization of carboxylic acid **654** then gave lactones **655** and **656** as a 1:2 mixture of diastereomers respectively.⁸¹ The *cis* and *trans* stereochemistry was deduced through interpretation of the ¹H NMR spectra of these compounds. The *trans* isomer demonstrates large axial-axial coupling for both H_a and H_b (Scheme 3.51). Alternatively, *cis* isomer **655** only experiences one of these large couplings. This deduction of stereochemistry agreed with that cited in the literature.

Scheme 3.51



Although the mixture of diastereomers could not be separated by flash column chromatography, lactones **655** and **656** were successfully partitioned by semi-preparative HPLC (Scheme 3.52). The subsequent conversion of these lactones to exocyclic enol ethers **624** and **625** was performed via Petasis olefination, albeit in moderate to low yield. It should be noted that the reaction of *trans*-lactone **656** was performed only once, and optimization of this transformation may lead to higher yields.

Scheme 3.52



Chiral Induction and Transfer Studies

With a variety of 2-methylenetetrahydropyrans in hand, studies were initiated to determine the effect of ring substitution on the diastereoselectivity of the carbonyl-ene reaction. All reactions were performed at room temperature with 5 to 20 mol% zinc(II) chloride according to optimized conditions previously determined for the carbonyl-ene reaction of exocyclic enol ethers.⁴⁷ The 2-methylenetetrahydropyran substrates were diluted to 0.5 M in THF, to which aldehydes (1.2 equivalents) were added. After zinc(II) chloride addition, the reaction was stirred from 2-12 hours depending on the reactivity of the aldehyde substrate used. The diastereoselectivity of each reaction was determined through integration analysis of resonances arising from either C_6 or C_2' hydrogen peaks in the respective product ^1H NMRs, although the major isomer in each case was not assigned.

The aldehyde components for this study were chosen to reflect anticipated differences in reactivity. These enophiles ranged from highly reactive ethyl glyoxylate **343** to aliphatic octyl aldehyde **495**, which has much less inherent reactivity. The high activation of ethyl glyoxylate **343** stems from the adjacent, strong electron-withdrawing group (CO_2Et), which increases the electrophilic nature of the compound by decreasing electron density at the carbonyl. The reduced electron density at this carbon center results in increased activation towards the ene reaction. *p*-Nitrobenzaldehyde **383** represents an enophile of intermediary reactivity. This

aromatic ring also pulls electron density from the carbonyl carbon, due to the presence of an electron withdrawing group on the aromatic ring, but to a much lesser extent than ethyl glyoxylate **343**. Octyl aldehyde **495** represents a non-activated aliphatic aldehyde that consequently has the lowest intrinsic reactivity of the group chosen. Due to these differences in reactivity, ene processes with activated aldehydes **343** and **383** were performed with 5 mole % zinc(II) chloride, whereas reactions involving non-activated aldehyde **495** were carried out with 20 mol % of the Lewis acid catalyst.

Initial diastereoselective studies focused on the influence of mono-substituted enol ethers **590-592** (Table 3.12). Enol ether **590** was first examined to evaluate the influence of a C₆ stereocenter on the diastereoselectivity of the carbonyl-ene reaction. The reaction of enol ether **590** with ethyl glyoxylate **343** was highly efficient, providing product **657** as a 1:1.1 mixture of diastereomers in 98% yield within a relatively short period of time (entry 1). The relative stereochemistry of the resulting isomers here, and in all cases, was not determined. The reaction with *p*-nitrobenzaldehyde **383** also provided the corresponding ene adduct in high yield within two hours, but as a 1:1 mixture of isomers. Lastly, non-activated octyl aldehyde **495** provided ene adduct **659** as a non-selective (1:1) mixture of diastereomers (entry 3). While all these reactions of C₆-benzyl-substituted 2-methylenetetrahydropyran **590** delivered the desired ene adducts in high yield, little to no selectivity was observed in each case. These results are in keeping with earlier studies performed in the Totah group (Scheme 3.37).⁶⁸

Exocyclic enol ether **591** was evaluated in turn to discover if selectivity can be induced from a C₅ stereocenter on the tetrahydropyran ring. The reaction between substrate **591** and all three aldehydes also proceeded well with ene adducts isolated in 80-88% yield (entries 4-6). These reactions showed only modest selectivity, with ratios of about 1:1.3 in each case.

Table 3.12: Carbonyl Ene Reactions of mono-Substituted 2-Methylenetetrahydropyrans

$ \begin{array}{c} \text{Ph-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH=CH}_2\text{-O} \\ \text{1:1.2} \end{array} + \text{H-C(=O)-R} \xrightarrow[\text{rt, THF 0.5M}]{\text{ZnCl}_2 \text{ (5-20 mol\%)}} \text{Ph-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH(OH)-CH}_2\text{-R} $						
Entry	Enol Ether	Aldehyde	Time (h)	Yield	dr	Product
1			2	98%	1.1:1	
2			2	94%	1:1	
3			12	83%	1:1	
4			2	80%	1.3:1	
5			2	88%	1.4:1	
6			12	80%	1.3:1	
7			2	88%	2.4:1	
8			2	92%	2.6:1	
9			12	76%	2.4:1	

The C₄-substituted enol ether **592** was finally examined with the same set of aldehydes. The yields ranged from 74-92% (entries 7-8), with the lowest yield obtained for the least activated substrate, octyl aldehyde **495** (entry 9). Note that this reaction (entry 9) was run only once, and the data does not demonstrate optimized yields. In these examples, mixtures of diastereomers were obtained as a ca. 1:2.5 ratio.

Though the observed selectivity was modest in every case, the higher selectivity demonstrated by the C₄-substituted substrate **592** (entry 7) as opposed to enol ethers **590** (entry 1) and **591** (entry 4) indicates that the proximity of a single pre-existing stereocenter to the site of hydrogen abstraction may influence reaction diastereoselectivity. Additionally, stereoselectivity is not dependent of the electronic nature of the aldehyde. For each of the enol ether substrates evaluated, observed diastereoselectivity remained constant regardless of the aldehyde used in the reaction (entries 1-3, 4-6, and 7-9).

As discussed earlier in this chapter, the mechanism for the carbonyl-ene reaction can range from a concerted to stepwise cationic process. Whether the mechanism is concerted, stepwise, or somewhere in-between, ene reactions involving Lewis acids undoubtedly develop a positive charge to some extent on the ene component.⁸² The concerted mechanism is capable of producing products of good stereoselectivity, since it is a single barrier process. Most carbonyl-ene reactions without large conformational constraints proceed through a mechanism with appreciable concerted character. If the Lewis acid-catalyzed carbonyl-ene reaction was purely a cationic process, many of the diastereoselective ene examples presented herein, most of which involve chair transition states, would not proceed selectively. Therefore the carbonyl-ene

reaction of 2-methylenetetrahydropyrans with aldehydes, catalyzed by zinc(II) chloride, is assumed to proceed in at least a partially concerted manner via chair-like transition states.

The presence of a single stereocenter on the exocyclic enol ether causes the tetrahydropyran ring to preferentially adopt a conformation favoring equatorial placement of the substituent. The aldehyde prefers approach from the tetrahydropyran face which bears the axial hydrogen for abstraction. The axial hydrogen is prone towards this process due to its favorable orbital alignment with the olefin pi electrons. Thus high selectivity was expected for the carbonyl-ene reaction of mono-substituted 2-methylenetetrahydropyrans, dictated by the conformation of the tetrahydropyran ring system. The low ratio of resulting isomers shows, however, that this is not the case.

In light of the poor selectivity observed, the transition state models were more closely examined. It is the face of the aldehyde approach that is believed to influence the stereochemistry of these systems. In these models, the Lewis acid can adopt either endo or exo chelation with the carbonyl oxygen. The endo conformer is predicted to be significantly higher in energy because of the non-bonding interactions between the relatively large metal and tetrahydropyran ring (Scheme 3.53). Therefore the transition state models for the ene reaction between 2-methylenetetrahydropyran and chelated aldehydes is typically expected to occur through endo transition states.

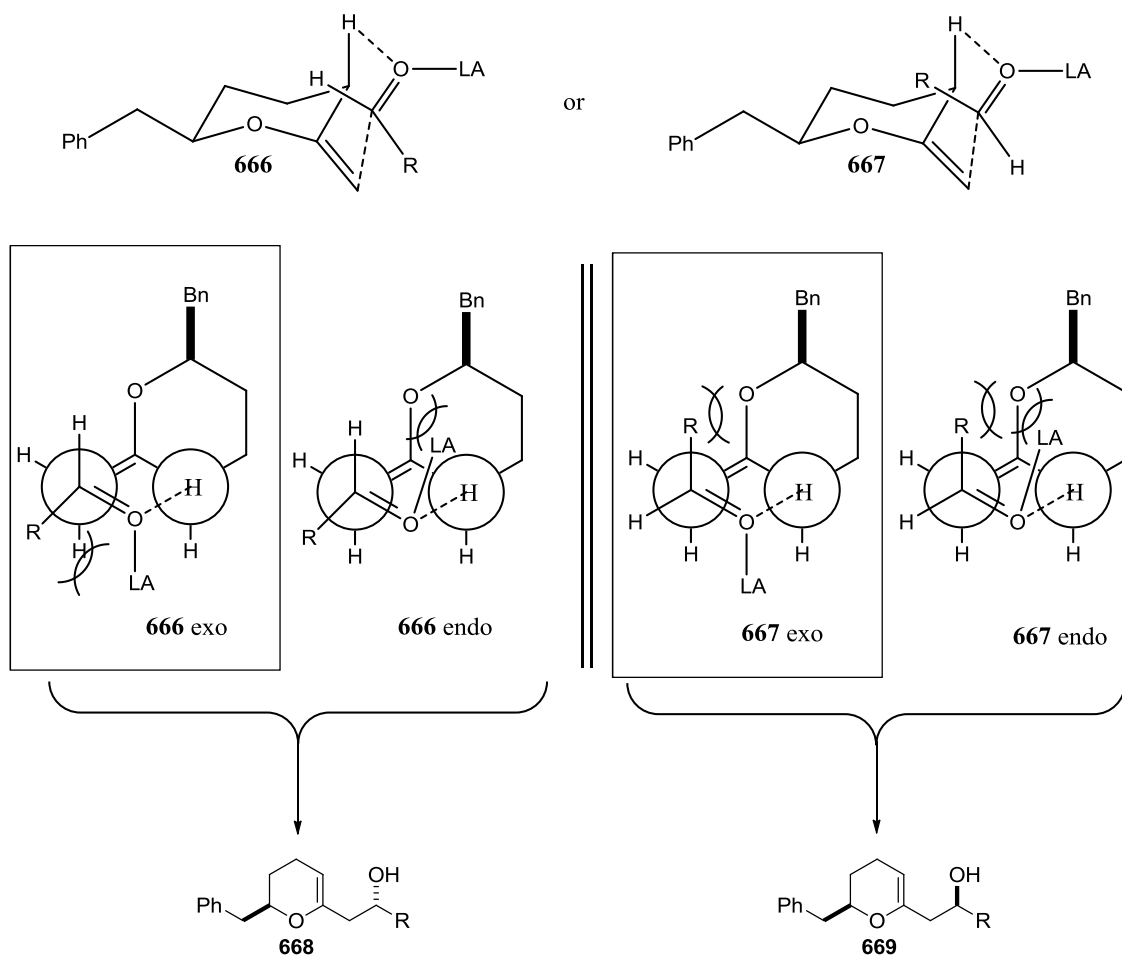
Approach of the aldehyde toward the 2-methylenetetrahydropyran can occur from either the re or si face (Scheme 3.53). Exposure of the re face is demonstrated in exo transition state **666**. Here, unfavorable, high energy 1,3 diaxial steric interactions (2.4 Kcal/mol) are avoided that develop between the aldehyde's R group and the ring oxygen as compared to the **667** endo transition state (Scheme 3.53). If the interaction between the aldehyde R group and the ring

oxygen was the only basis for stereochemical preference, high ratios of diastereomer **668** would prevail in upwards of ca. 98:2 according to equations 3.1-3.2.

$$K = e^{-(G/RT)} \quad (\text{Equation 3.1})$$

$$K = \frac{[\mathbf{669}]}{[\mathbf{668}]} = \frac{[\mathbf{669}]}{100-[\mathbf{669}]} \quad (\text{Equation 3.2})$$

Scheme 3.53

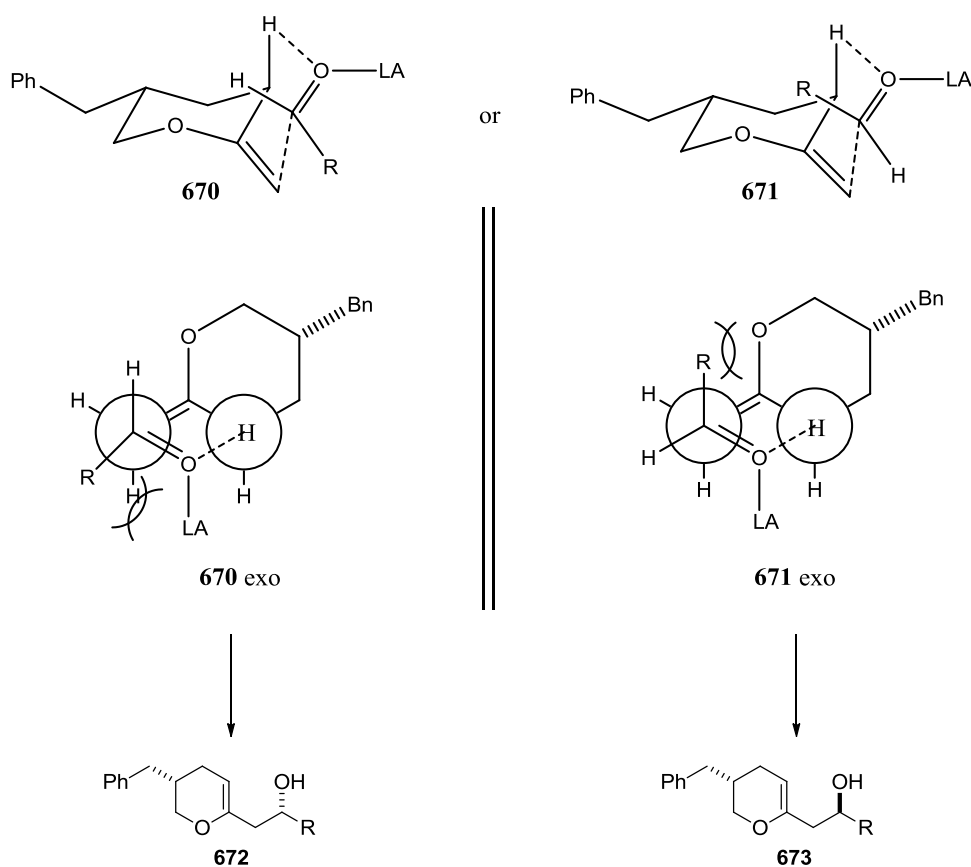


Clearly the discrepancy between calculated ratios and the low ratio of stereoisomers obtained for this reaction (Table 3.12, entries 1-3) indicates other steric influences are at hand, namely non-bonding interactions between the chelated Lewis acid and the pendent aldehyde group. Therefore when the aldehyde approaches from the *re* face, this Lewis acid-aldehyde R

group interaction is the predominant steric influence (**666** exo, Scheme 3.53). Conversely, the transition state where the aldehyde enters from the si face (**667** exo) experiences the steric repulsion between the aldehyde R group and the ring oxygen. The ratio observed (1:1) indicates that the severity of these steric repulsions is comparable.

Application of these transition state models to the reactions of enol ethers **591** and **592** shows similar analyses (Schemes 3.54 and 3.55 respectively). Ene reactions between 2-

Scheme 3.54

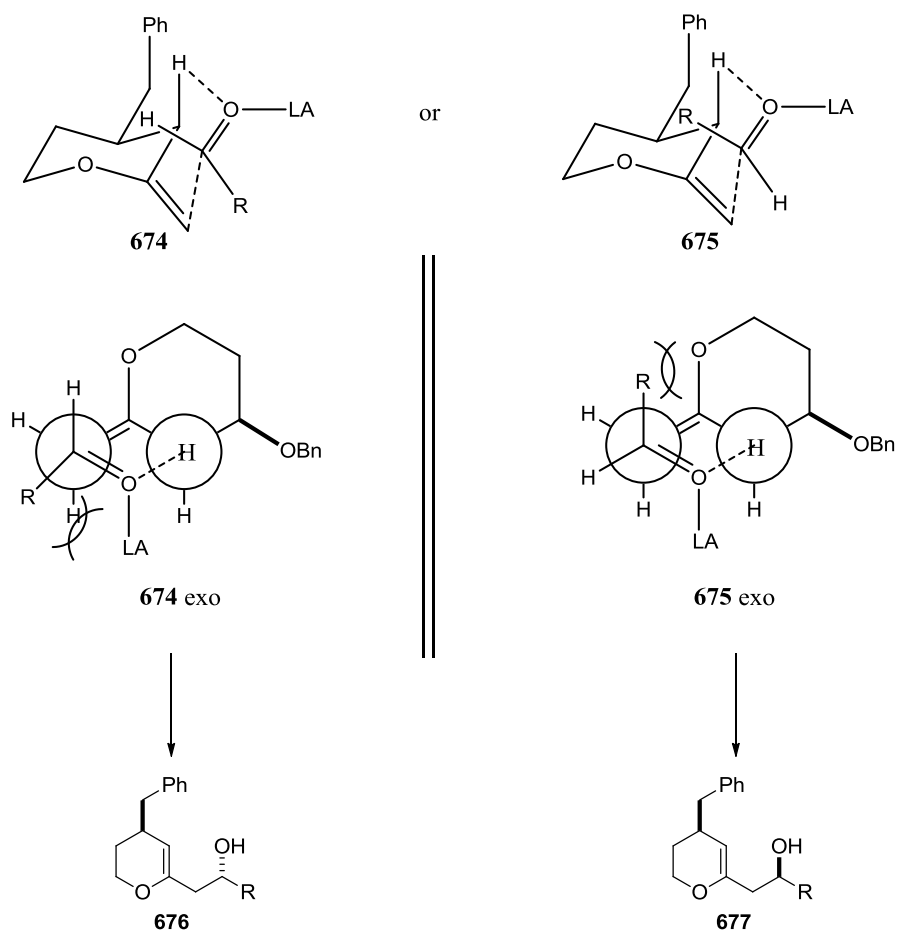


methylenetetrahydropyran **591** and aldehydes are expected to proceed through either exo transition state **670** or **671**, producing products **672** and **673** respectively. Both transition states contain the same steric interferences that were exhibited by enol ether **590**. In turn, analysis of

the transition states associated with enol ether **592** (Scheme 3.55) illustrates that the same stereochemical influences are present in this system.

The transition state structures for enol ethers **590**, **591**, and **592** all show very similar energies and as such, low diastereoselectivity is observed for these processes. Although it is true that selectivity improves as the chiral center nears the site of hydrogen abstraction, a 2.6:1 ratio

Scheme 3.55



(at best) is very modest and only represents a small energy difference between transition state configurations. Prediction of the major isomer is difficult in these cases based on this transition state evaluation.

The low level of stereinduction derived from mono-substituted 2-methylenetetrahydropyrans proved disappointing. The diastereoselectivity of the reaction may be improved through use of di-substituted exo enol ethers, especially in those substrates with axial substituents. These groups may have an influence on the enophile approach. Secondly, di-substituted 2-methylenetetrahydropyrans were used to evaluate the extent of chirality transfer resulting from 2-methylenetetrahydropyran C₃ stereocenters.

The results of the diastereoselective ene reaction with enol ethers **622-625** are shown in Table 3.13. Reaction of 2-methylenetetrahydropyran **622** with activated aldehydes ethyl glyoxylate **343** and *p*-nitrobenzaldehyde **383** provided the desired ene adducts in high yield (entries 1 and 2). The diastereomer products produced in these reactions were observed as ca. 1.4:1 ratios, however, as in the mono-substituted 2-methylenetetrahydropyran studies, the identity of the major and minor isomers was not determined. Reaction of the same enol ether with octyl aldehyde **495** resulted in moderate yields of corresponding ene adduct **680** (entry 3). Although it is true that this enophile is less reactive in comparison to ethyl glyoxylate **343** and *p*-nitrobenzaldehyde **383**, this reaction was only performed twice and does not represent optimized yields. Diastereomeric ratios were not obtained for ene product **680**, because analysis of the ¹H NMR resonances did not reveal the ratio of isomers. The individual peaks of each diastereomer could not be resolved, even after altering NMR sample solvent systems. The solvents tested for peak resolution included CDCl₃, C₆D₆, D-methanol, D-acetonitrile, D-acetone, D-ethanol, and mixtures thereof.

Examination of exocyclic enol ether **623** demonstrated that high yields of ene adducts **681** and **682** could be obtained with aldehydes **343** and **383** respectively (entries 4 and 5). The reaction with ethyl glyoxylate **343** produced ene adducts as a 2.6:1 ratio, whereas the reaction

Table 3.13: Carbonyl Ene Reactions of di-Substituted 2-Methylenetetrahydropyrans

Entry	Enol Ether	Aldehyde	Time (h)	Yield	dr	product
1			2	100%	1.3:1	
2	622		2	94%	1.4:1	
3	622		11	49%	NA	
4			2	97%	2.6:1	
5	623		2	100%	3.5:1	
6	623		11	74%	1.7:1	
7			2	60%	2.1:1	
8			2	51%	1:2.3	

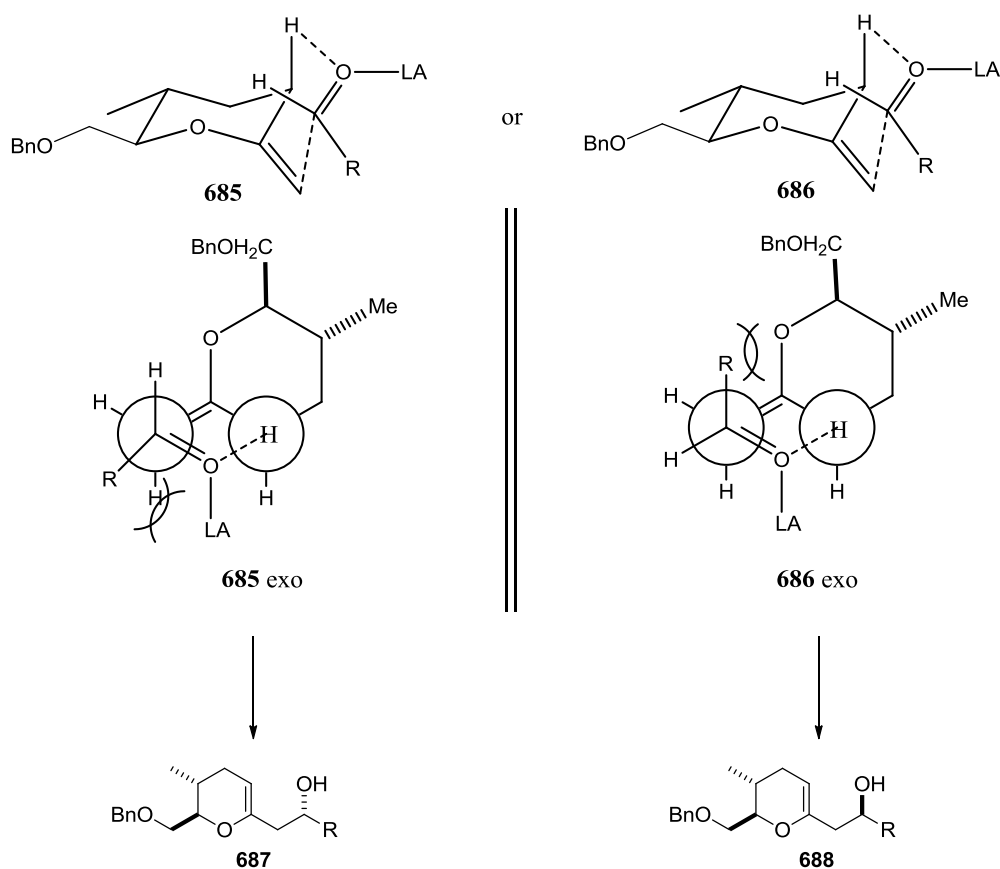
with *p*-nitrobenzaldehyde **383** yielded products in a 3.5:1 ratio. Alternatively, the reaction with octyl aldehyde **495** produced product **683** in moderate yield with relatively low stereoselectivity (1:1.7 ratio of isomers, entry 6).

Exocyclic enol ethers **624** and **625** were studied last to determine how both axial or equatorial substituents and C₃ chiral centers affect stereoselectivity. Subjection of 2-methylenetetrahydropyrans **625** and **626** to highly activated ethyl glyoxylate **343** resulted in modest yields of the same carbonyl-ene adduct **684** (entries 7 and 8). The low yields observed for this process are in keeping with earlier studies performed in the Totah group that demonstrated how 2-methylenetetrahydropyran C₃ substituents can decrease carbonyl-ene product yields (Table 3.5).⁶⁸ The ratio of products in each case complimented one another. The ¹H NMR product resonances indicated the given diastereomer ratios through evaluation of the C₆ proton integrations. The ¹H NMR spectra of both reactions were the same except the integrations of the resolved C₆ protons were opposite in magnitude. Therefore it is concluded that both reactions result in the same products, but the major diastereomer produced in each case was different.

The ene reactions of enol ether **622** only demonstrated low levels of selectivity (1:1.4-1:1.3 dr, entries 1 and 2, Table 3.13), which was similar to that observed for C₅-substituted enol ether **591** (entries 4-6, Table 3.12). Therefore, the equatorial C₅ methyl substituent on enol ether **622** most likely has a similar effect as the equatorial benzyl group on enol ether **591**. Review of exo transition states **685** and **686** (Scheme 3.56) indicate the same steric interactions are at play as were in the transition states associated with enol ether **591** (Scheme 3.54). Transition state **685** suffers from steric repulsion between the chelated Lewis acid and pendant aldehyde group, whereas transition state **686** experiences non-bonding interactions between the aldehyde R group and the ring oxygen. It is not clear from the presented transition states which isomer is preferentially produced or how the C₅ chiral center plays part, but as the low selectivity shows, only a small difference in energy exists between the two transition states.

The ene reactions of enol ether **623**, on the other hand, shows higher levels of diastereoselectivity in the resulting products (3.5:1-1.7:1, entries 4-5, Table 3.13). The difference in observed selectivity can be rationalized in terms of steric repulsion between the axial tetrahydropyranyl methyl group and incoming enophile (Scheme 3.57). Thus transition state **689** only possesses one major non-bonding interaction between the aldehyde group and

Scheme 3.56

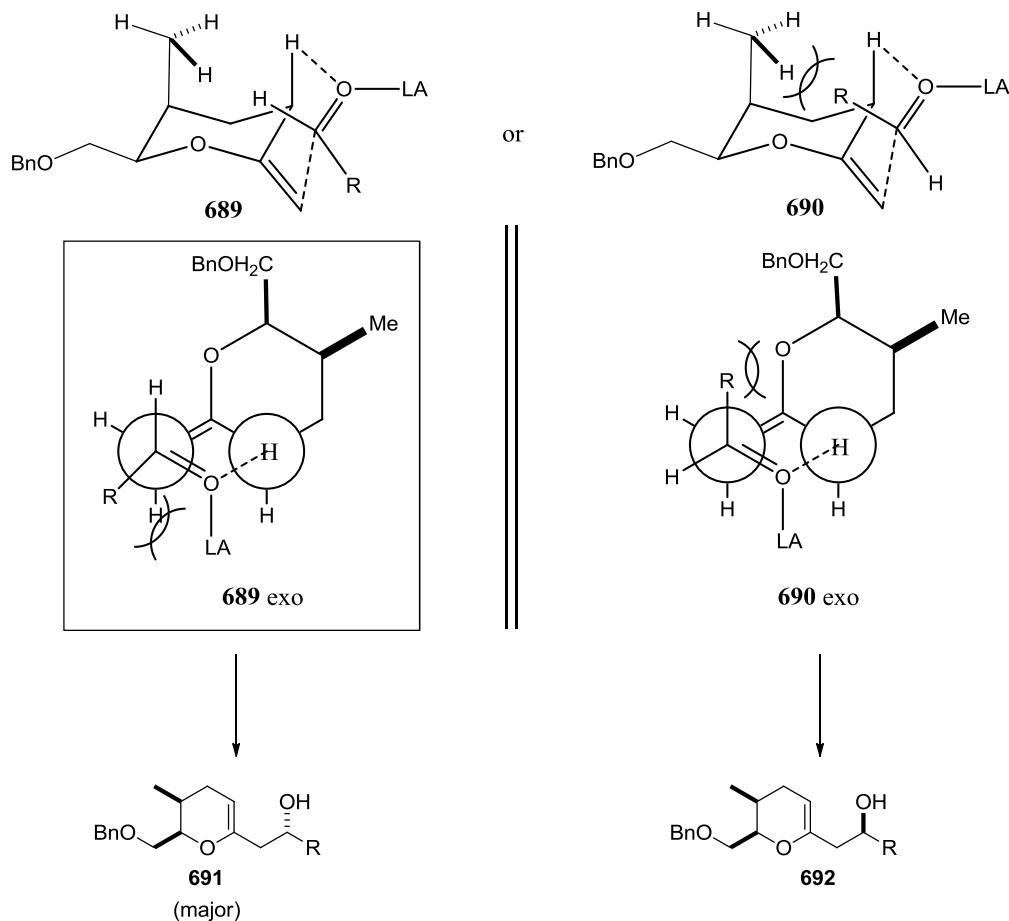


Lewis acid, whereas transition state **690** contains two large steric repulsions between the aldehyde R group and both the axial methyl and ring oxygen. This leads to the prediction of diastereomer **691** as the major product.

While there is no change in the level of stereoselectivity based on aldehyde stereoelectronics, a trend in enophile sterics is demonstrated. As the steric bulk of the aldehyde

substrate increased near to the carbonyl center, the ratio of isomers changed directly. This is shown by octyl aldehyde **495**, the smallest of the aldehydes tested, producing the lowest ratio of diastereomers (1.7:1, entry 6, Table 3.13). In turn ethyl glyoxylate **343** delivered less selectivity (2.6:1, entry 4) than the largest aldehyde tested, *p*-nitrobenzaldehyde **383** (3.5:1, entry 5). This

Scheme 3.57



trend illustrates that as the size of enophile increases, a larger effect is experienced by transition state **690** versus transition state **689**.

Both enol ethers **624** and **625** produce the same product **684** through the carbonyl-ene reaction with ethyl glyoxylate **343**. Similar diastereomer ratios are obtained for both enol ether **624** and **625**, however, the major diastereomers formed in each case are different, as was

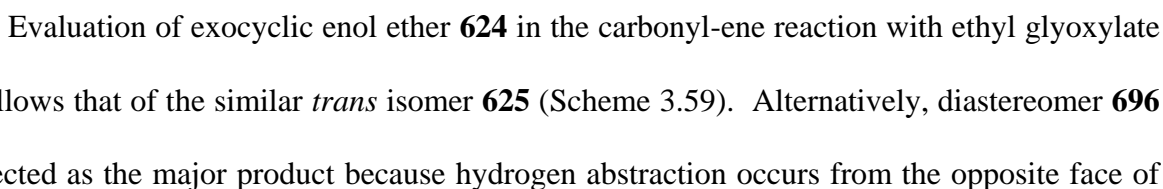
indicated in the ^1H NMR spectra of each separate reaction. Enol ether **624** is expected to provide isomer **695** as the major product (Scheme 3.58), while enol ether **625** is anticipated to produce larger quantities of isomer **696** (Scheme 3.59).

The transition states associated with enol ethers **624** and **625** are perceived to proceed with the abstractable hydrogen in the axial position due to favorable orbital alignment with the olefin pi bond. In these systems, the factors associated with selectivity include the face of enophile approach and exo versus endo chelation of the Lewis acid. Steric influences of axial versus equatorial substituents on the tetrahydropyran ring are indicated to be of little consequence since the ratio of diastereomers obtained from the two reactions is similar in magnitude.

Substrate **625** is predicted to produce diastereomer **695** through analysis of transition states **693** and **694**. Review of transition state **693** indicates that the exo transition state exhibits steric repulsion between the pendant aldehyde group and the chelated Lewis acid. This transition state differs from all those discussed so far, because the Lewis acid also experiences non-bonding interactions with the tetrahydropyranyl C₃ equatorial methyl. Evaluation of exo transition state **694**, where the aldehyde approaches from the *re* face indicates this same steric repulsion between the two groups in addition to that between the pendant aldehyde group and the tetrahydropyran ring oxygen.

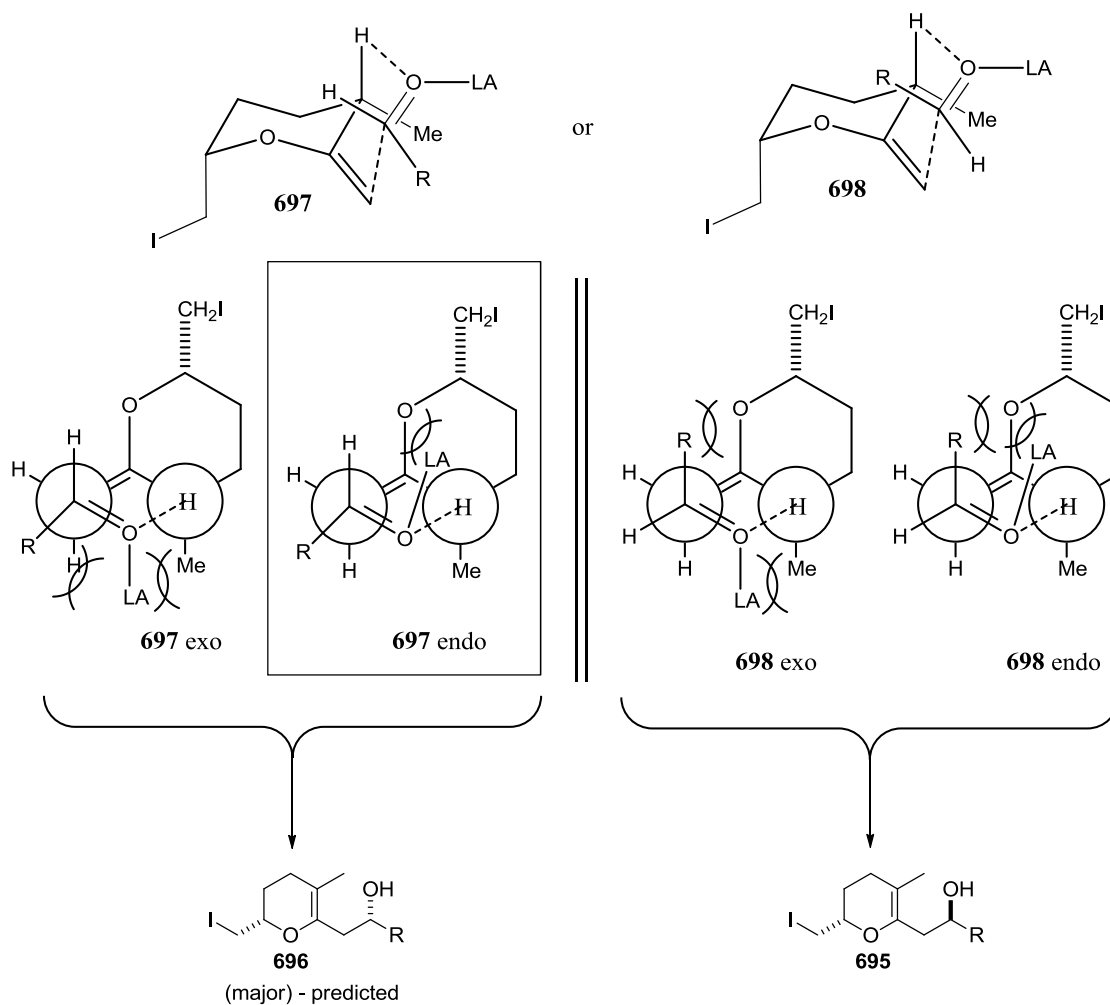
The endo transition state **693** alleviates two non-bonding interactions between the Lewis acid and both the aldehyde R group and tetrahydropyran C₃ methyl. However, this endo transition state experiences a large interaction between the Lewis acid and tetrahydropyran ring. Contrarily, endo transition state **694** only alleviates one steric repulsion between the Lewis acid and tetrahydropyran methyl, while developing a new, larger interaction between the Lewis acid

Scheme 3.58



the tetrahydropyran ring. Here, the C₆ axial iodomethyl group has little to no effect on the stereoselectivity of the reaction because aldehyde approach is from the face opposite the substituent.

Scheme 3.59



3.4 Conclusions

The carbonyl-ene reaction of 2-methylenetetrahydropyrans, with a variety of substitution patterns about the tetrahydropyran ring, proceeded with good to excellent yields with both activated and non-activated aldehydes. Mono-substitution at the C₆, C₅, and C₄ positions on the tetrahydropyran ring only produced modest selectivity of the products at best. Prediction of the

major isomers in these systems is not straightforward from review of the corresponding transition states, although selectivity seemed to increase as the chiral center increased in proximity to the site of hydrogen abstraction.

The diastereoselectivity exhibited by reactions of di-substituted 2-methylenetetrahydropyrans followed the results of mono-substituted examples in that only moderate to low ratios of products resulted. Nonetheless, evaluation of exo enol ethers **622** and **623** demonstrated that the presence of axial substituents on the tetrahydropyran ring can cause higher product discrimination (ratios of 1.4:1 versus upwards of 3.5:1). The product ratios of these axial systems, which ranged from 1.7:1 to 3.5:1, seem to be based on aldehyde sterics, where the larger the steric bulk about the carbon alpha to the carbonyl, the larger the ratio of resulting isomers.

Alternatively, examination of enol ethers **624** and **625** demonstrates that axial influences can be negligible, especially when these substituents are opposite the reactive tetrahydropyranyl face. These conflicting results show the great complexity of these systems, and how selectivity is highly substrate dependent. The assessment of enol ethers **624** and **625** confirmed, however, that C₃ substituents are capable of slight stereinduction exhibited by the 2.1:1 ratio of products.

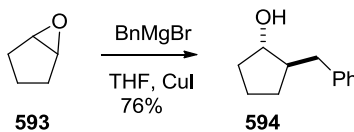
The compilation of these results indicates that simple substitution about the ring of 2-methylenetetrahydropyrans is not likely to cause high levels of stereinduction in the carbonyl-ene reaction. Instead, the use of chiral catalysis may be more effective towards this end.

3.5 Experimental

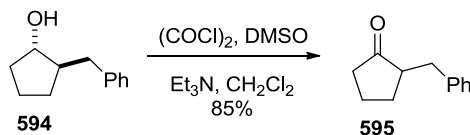
General Methods:

All air sensitive reactions were performed in oven dried glassware under an atmosphere of argon. Reaction solvents were dried over CaH_2 (benzene, dichloromethane), or sodium/benzophenone ketyl (tetrahydrofuran, diethyl ether) and were distilled just prior to use. All other reagents were reagent grade and purified as necessary. Analytical thin layer chromatography was performed on EM silica gel 60 F254 glass plates (0.25 mm). Visualization of analytical thin layer chromatography was achieved using UV absorbance (254 nm), vanillin, and ceric ammonium molybdate stains. Melting points were recorded using an Electrothermal melting point apparatus and are uncorrected. Flash column chromatography was performed using SiliaFlash P60 silica gel (40-60 Å) from SiliCycle, Inc. ^1H NMR spectra were recorded on a Bruker Avance DPX-300 (300 MHz) spectrometer. Chemical shifts are reported in ppm, downfield from tetramethylsilane using residual CHCl_3 as the internal standard (δ 7.27 ppm). ^{13}C NMR spectra were recorded on a Bruker Avance DPX-300 (75 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm, downfield from tetramethylsilane using residual CHCl_3 as the internal standard (δ 77.0 ppm). IR spectra were obtained with a Thermo Nicolet IR-100 spectrometer on NaCl plates. Elemental Analyses were performed by Complete Analysis Laboratories, Inc.; Parsippany, NJ. High resolution mass spectra were obtained using the positive ion electrospray mode on a Bruker 12 Tesla APEX-Qe FTICR-MS with an Apollo II ion source at Old Dominion University, Norfolk, VA.

Experimental Procedures:

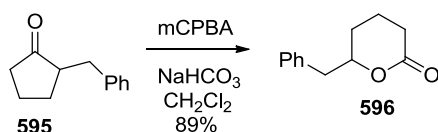


Alcohol 594. Benzyl magnesium bromide 1.0 M in diethyl ether (25.0 mL, 25.0 mmol) was added to a dried flask and stirred along with copper iodide (0.261g, 1.37 mmol). Cyclopentene oxide **593** (1.75g, 20.8 mmol) was dissolved in diethyl ether (3.5 mL) and added via dropwise addition to the reaction flask. The reaction mixture stirred for two hours before being quenched with aqueous ammonium chloride (15 mL). The layers were separated and the aqueous layer was extracted with additional diethyl ether (3 x 30 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (SiO₂; hexanes:EtOAc, 4:1-2:1) yielded desired alcohol **594** as a colorless oil (2.78g, 76%). TLC: R_f = 0.43 (hexanes:EtOAc, 2:1). ¹H NMR data for this compound agreed with the known literature values.⁸³ ¹H NMR (CDCl₃, 300 MHz): δ 7.24 (5H, m), 3.30 (1H, m), 3.18 (1H, dd, *J* = 4.1, 14.2 Hz), 2.35 (1H, dd, *J* = 14.1, 7.9 Hz), 1.44 (10H, m).

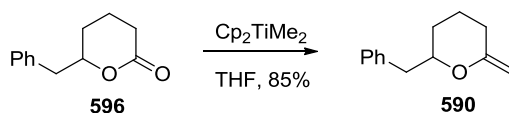


Ketone 595. Oxalyl chloride (2.00 mL, 23.7 mmol) was dissolved in dichloromethane (77 mL) and cooled to -78°C. DMSO (3.59 mL, 50.5 mmol) was subsequently added via dropwise addition over a period of fifteen minutes. The reaction mixture stirred for an additional fifteen minutes after which alcohol **594** (2.78g, 15.8 mmol) was added in dichloromethane (13 mL). The reaction mixture stirred for an additional thirty minutes after which triethylamine (11.0 mL, 78.9 mmol) was added by dropwise addition. The reaction was then warmed to room temperature and stirred for an additional hour. Water was added (100 mL). The organic and

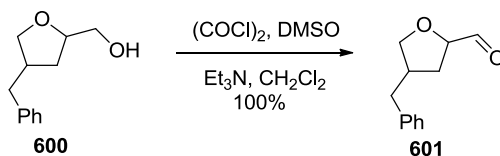
aqueous layers were separated and the aqueous layer was extracted with dichloromethane (3 x 70 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (SiO₂; hexanes:EtOAc, 5:1) yielded desired ketone **595** as a colorless oil (2.33g, 85%) ¹H NMR data for this compound agreed with the known literature values.⁸⁴ TLC: R_f = 0.76 (hexanes:EtOAc, 2:1). ¹H NMR data for this compound agreed with the known literature values.⁸⁵ ¹H NMR (CDCl₃, 300 MHz): δ 7.24 (5H, m), 3.16 (1H, dd, *J* = 13.8, 4.1 Hz), 2.55 (1H, dd, *J* = 13.7, 9.5 Hz), 2.36 (2H, m), 2.11 (2H, m), 1.96 (1H, m), 1.75 (1H, m), 1.58 (1H, m).



Lactone 596. mCPBA (1.03g, 4.16 mmol) and sodium bicarbonate (1.38g, 16.5 mmol) were added to a solution of ketone **595** (0.630g, 3.62 mmol) in dichloromethane (22mL). The reaction was stirred for 60 hours and then washed with saturated sodium bicarbonate (2 x 20 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (20 mL). The combined organic layers were dried with MgSO₄, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (SiO₂; hexanes:EtOAc 2:1) yielded the desired lactone **596** as a colorless oil (0.617g, 89%). TLC: R_f = 0.25 (hexanes:EtOAc, 2:1). ¹H NMR data for this compound agreed with the known literature values.⁸⁶ ¹H NMR (CDCl₃, 300 MHz): δ 7.28 (5H, m), 4.50 (1H, m), 3.10 (1H, dd, *J* = 13.8, 5.8 Hz), 2.88 (1H, dd, *J* = 13.8, 7.0 Hz), 2.58 (1H, m), 2.42 (1H, m), 1.86 (3H, m), 1.53 (1H, m).

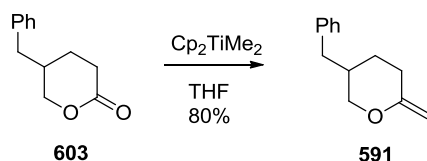


Enol Ether 590. To a solution of lactone **596** (0.100g, 0.526 mmol) in 3 mL THF was added Cp_2TiMe_2 (2.10 mL of a 0.5M solution in THF, 1.05 mmol). The resulting mixture was warmed to reflux and stirred for 20 h in the dark. The solution was then cooled to room temperature, concentrated *in vacuo*, and the resulting residue triturated with hexanes. (100 mL). The hexanes solution was filtered through celite and concentrated again. The residue was purified via flash chromatography (SiO_2 ; hexanes:triethylamine, 19:1) to afford the exocyclic enol ether **590** as a yellow oil (0.085 g, 85%). TLC: R_f = 0.70 (hexanes: EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 7.27 (5H, m), 4.34 (1H, d, J = 1.3 Hz), 4.08 (1H, d, J = 1.6 Hz), 3.85 (1H, m), 3.04 (1H, dd, J = 13.6, 6.1 Hz), 2.74 (1H, dd, J = 13.6, 7.1 Hz), 2.23 (2H, m), 1.64 (4H, m). ^{13}C NMR (CDCl_3 , 75 MHz): δ 159.9 (C), 139.5 (C), 128.9 (CH), 128.4 (CH), 126.1 (CH), 91.1 (CH_2), 73.6 (CH_2), 38.4 (CH_2), 36.6 (CH_2), 29.0 (CH_2), 28.3 (CH_2). IR (film): 3027, 2928, 1654 cm^{-1} .

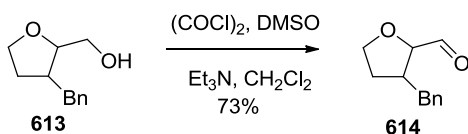


Aldehyde 601. Oxalyl chloride (0.0950 mL, 1.12 mmol) was dissolved in dichloromethane (3.6 mL) and cooled to -78°C . DMSO (0.170 mL, 2.40 mmol) was added to the reaction via dropwise addition over a period of fifteen minutes. Thereafter the reaction mixture was left to stir an additional fifteen minutes, after which alcohol **600** (0.144g, 0.749 mmol) was slowly added as a solution in dichloromethane (0.60 mL). The reaction mixture stirred for thirty minutes, and then triethylamine (0.530 mL, 3.75 mmol) was added via dropwise addition. The reaction was warmed to room temperature and stirred for an additional hour. Water was added (3 mL) and the organic and aqueous layers were separated. Aqueous layers were extracted with

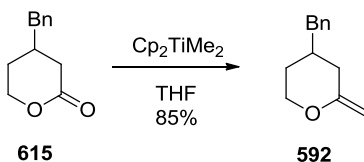
dichloromethane (3 x 10 mL). Combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (SiO₂; hexanes:EtOAc, 3:1) yielded the desired aldehyde **601** as a colorless oil (0.142g, 100%) ¹H NMR data agreed with the known literature values for this compound.¹⁴ TLC: R_f = 0.34 (hexanes:EtOAc, 2:1). ¹H NMR (300 MHz, CDCl₃): δ 9.69 (1H, dd, *J* = 12.5, 1.6 Hz), 7.24 (5H, m), 4.40 (0.6H, m), 4.29 (0.4H, dt, *J* = 8.1, 1.7 Hz), 4.03 (1H, m), 3.66 (1H, m), 2.53 (1H, m), 2.28 (1H, m), 2.14 (1H, m), 1.92 (1H, m), 1.71 (1H, m).



Enol ether 591. To a solution of lactone **603** (0.095g, 0.499 mmol) in 3 mL THF was added Cp₂TiMe₂ (2.00 mL of a 0.5M solution in THF, 0.999 mmol). The resulting mixture was warmed to reflux and stirred for 20 h in the dark. The solution was then cooled to room temperature, concentrated *in vacuo*, and the resulting residue triturated with hexanes. (100 mL). The hexanes solution was filtered through celite and concentrated again. The residue was purified via flash chromatography (SiO₂; hexanes:triethylamine, 19:1) to afford the exocyclic enol ether **591** as a yellow oil (0.075 g, 80%). TLC: R_f = 0.87 (hexanes: EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 7.24 (5H, m), 4.33 (1H, s), 4.07 (1H, d, *J* = 1.4 Hz), 4.00 (1H, ddd, *J* = 10.8, 4.2, 1.8 Hz), 3.43 (1H, t, *J* = 10.3 Hz), 2.59 (1H, dd, *J* = 13.5, 7.3 Hz), 2.48 (1H, dd, *J* = 13.5, 7.3 Hz), 2.33 (1H, dt, *J* = 14.3, 4.7 Hz), 2.11 (2H, m), 1.84 (1H, m), 1.33 (1H, m). ¹³C NMR (CDCl₃, 75 MHz): δ 159.9 (C), 139.5 (C), 128.9 (CH), 128.4 (CH), 126.1 (CH), 91.1 (CH₂), 73.6 (CH₂), 38.4 (CH₂), 36.6 (CH), 29.0 (CH₂), 28.3 (CH₂). IR (film): 3028, 2929, 1654 cm⁻¹.

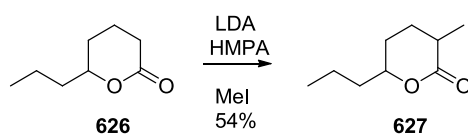


Aldehyde 614. Oxalyl chloride (0.132 mL, 1.56 mmol) was dissolved in dichloromethane (5.1 mL) and cooled to -78°C . DMSO (0.24 mL, 3.33 mmol) was added to the reaction via dropwise addition over a period of fifteen minutes. Thereafter the reaction mixture was left to stir an additional fifteen minutes, after which alcohol **613** (0.200g, 1.04 mmol) was slowly added as a solution in dichloromethane (0.83 mL). The reaction mixture stirred for thirty minutes, and then triethylamine (0.73 mL, 5.20 mmol) was added via dropwise addition. The reaction was warmed to room temperature and stirred for an additional hour. Water was added (3 mL) and the organic and aqueous layers were separated. Aqueous layers were extracted with dichloromethane (3 x 10 mL). Combined organic layers were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification via flash column chromatography (SiO_2 ; hexanes:EtOAc, 3:1) yielded the desired aldehyde **614** as a colorless oil (0.146g, 73%). ^1H NMR data agreed with the known literature values for this compound.¹⁴ TLC: $R_f = 0.42$ (hexanes:EtOAc, 2:1). ^1H NMR (300 MHz, CDCl_3): δ 9.78 (0.8H, d, $J = 2.2$ Hz), 9.55 (0.2H, d, $J = 1.9$ Hz), 7.25 (5H, m), 4.33 (1H, dd, $J = 7.6, 2.2$ Hz), 4.21 (0.8H, dt, $J = 8.1, 4.7$ Hz), 4.08 (0.2H, m), 3.93 (1H, m), 2.88 (2H, m), 2.46 (1H, m), 1.99 (1H, m), 1.74 (1H, m).



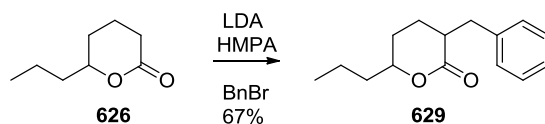
Enol ether 592. To a solution of lactone **615** (0.051g, 0.269 mmol) in 1.5 mL THF was added Cp_2TiMe_2 (1.07 mL of a 0.5M solution in THF, 0.537 mmol). The resulting mixture was warmed to reflux and stirred for 20 h in the dark. The solution was then cooled to room temperature,

concentrated *in vacuo*, and the resulting residue triturated with hexanes. (100 mL). The hexanes solution was filtered through celite and concentrated again. The residue was purified via flash chromatography (SiO₂; hexanes:triethylamine, 19:1) to afford the exocyclic enol ether **592** as a yellow oil (0.043 g, 85%). TLC: R_f = 0.79 (hexanes: EtOAc, 10:1). ¹H NMR (CDCl₃, 300 MHz): δ 7.24 (5H, m), 4.34 (1H, s), 4.12 (1H, ddd, J =11.1, 4.5, 3.0 Hz), 4.04 (1H, s), 3.61 (1H, m), 2.60 (2H, m), 2.30 (1H, m), 1.92 (1H, m), 1.54 (3H, m). ¹³C NMR (CDCl₃, 75 MHz): δ 159.4 (C), 139.6 (C), 129.1 (CH), 128.3 (CH), 126.1 (CH), 91.7 (CH₂), 68.7 (CH₂), 42.8 (CH₂), 36.5 (CH), 35.6 (CH₂), 31.2 (CH₂). IR (film): 3067 (w), 2932 (m), 1650 (m) cm⁻¹.

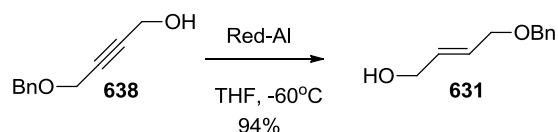


Tetrahydro-3-methyl-6-propyl-2H-pyran-2-one 627. Distilled diisopropylamine (0.27 mL, 1.94 mmol), diluted with THF (1.5 mL), was cooled to 0°C, and nBuLi (0.78mL, 1.94 mmol) was added by dropwise addition. The reaction mixture was cooled to -78°C and stirred for 30 minutes. Octanolactone **626** (0.23g, 1.62 mmol) was dissolved in THF (1.5 mL) and added dropwise to the solution. The reaction mixture was stirred an additional 30 minutes at which time a mixture of MeI (0.30g, 2.10 mmol), HMPA (0.39 mL, 2.26 mmol) and THF (1 mL) were added. The reaction was warmed to -40°C for three hours and then stirred at room temperature overnight. The reaction mixture was washed with saturated NH₄Cl and diluted with ether. The organic layer was separated from the aqueous. The aqueous layer was extracted with ethyl acetate (3 x 5 mL). Organic layers were combined, dried over MgSO₄, filtered, and concentrated. Column chromatography (SiO₂; 3:1, hexanes:EtOAc) afforded lactone **627** as a colorless oil (0.170g, 67%) in a 1:1 mixture of diastereomers. Compound identity was determined by ¹H NMR⁸⁷. TLC: R_f = 0.24 (10:1, hexanes:EtOAc) ¹H NMR (CDCl₃, 300 MHz):

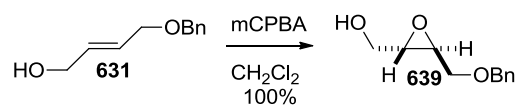
δ 4.30 (1H, m), 2.60 (0.6H, m), 2.45 (0.4H, m), 1.99 (2H, m), 1.55 (6H, m), 1.30 (1.2H, d, $J = 7.1$ Hz), 1.22 (1.8H, d, $J = 6.8$ Hz), 0.94 (3H, t, $J = 7.1$ Hz).



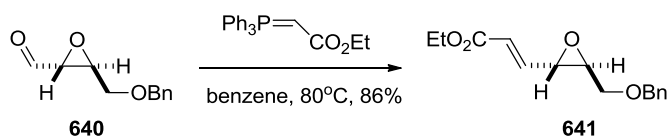
Tetrahydro-3-benzyl-6-propyl-2H-pyran-2-one 629. Distilled diisopropylamine (0.27 mL, 1.94 mmol), diluted with THF (1.5 mL), was cooled to 0°C, and nBuLi (0.78mL, 1.94 mmol) was added by dropwise addition. The reaction mixture was cooled to -78°C and stirred for 30 minutes. Octanolactone **626** (0.23g, 1.62 mmol) was dissolved in THF (1.5 ml) and added dropwise to the solution. The reaction mixture was stirred an additional 30 minutes at which time a mixture BnBr (0.36g, 2.10 mmol), HMPA (0.39 mL, 2.26 mmol) and THF (1 mL) were added. The reaction was warmed to -40°C for three hours and then stirred at room temperature overnight. The reaction mixture is washed with saturated NH₄Cl and diluted with ether. The organic layer is separated from the aqueous. The aqueous layer was extracted with ethyl acetate (3 x 5 mL). Organic layers were combined, dried over MgSO₄, filtered, and concentrated. Column chromatography (SiO₂, 30:1 hexanes/EtOAc) afforded lactone **629** as a colorless oil (0.203g, 54%) in a 2:1 mixture of diastereomers. TLC: $R_f = 0.76$ (2:1, hexanes:EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 7.26 (5H, m), 4.25 (1H, m), 3.41 (0.66H, dd, $J = 13.6, 4.0$ Hz), 3.35 (0.33H, dd, $J = 13.5, 4.0$ Hz), 2.72 (2H, m), 1.86 (2H, m), 1.50 (6H, m), 0.93 (3H, t, $J = 10.2$ Hz). ¹³C NMR (CDCl₃, 300 MHz): δ 175.2, 173.1, 139.0, 138.8, 129.1, 129.0, 128.4, 126.3 (2), 81.3, 77.7, 42.5, 40.0, 38.2, 37.6, 37.2, 36.7, 28.7, 26.3, 24.9, 24.6, 22.5, 18.2, 17.9, 13.7. IR (film): 3063, 3028, 2959, 1735, 1603 cm⁻¹.



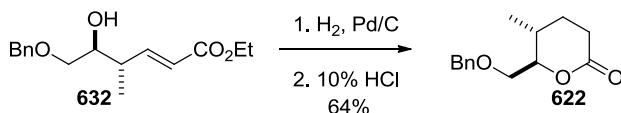
Alkene 631. Alkene **631** was made by dissolving Red-Al® (13.21g, 42.5 mmol) in THF (160 mL). The reaction mixture was cooled to -60°C , and a mixture of alkyne **638** in THF (160 mL) was added dropwise via cannula. After stirring for six hours at -60°C , Rochelle's salt was added and allowed to stir for an additional hour. The organic layer and aqueous layers were separated, and the aqueous layer was extracted with ether (3 x 80 mL). Organic layers were combined and washed with a saturated, aqueous sodium potassium tartrate solution. Drying of the organic layers with MgSO_4 was followed by filtration, concentration, and purification by flash chromatography (SiO_2 , 7:1-2:1, hexanes/ethyl acetate) to yield olefin **631** as a colorless oil (5.49g, 94%). ^1H NMR data agrees with that previously published for this compound.⁸⁸ TLC: R_f = 0.21 (hexanes:EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 7.32 (5H, m), 5.88 (2H, m), 4.53 (2H, s), 4.15 (2H, m), 4.04 (2H, dd, J = 4.3, 1.5 Hz), 2.01 (1H, s).



Epoxide 639. Epoxide **639** was manufactured from alkene **631** (8.13g, 45.62 mmol) and 70% mCPBA (16.87g, 68.42 mmol) by literature procedure to yield a solid white product.⁷⁰ ^1H NMR data for this compound agreed with the known literature values.⁸⁹ TLC: R_f = 0.33 (hexanes:EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 7.35 (5H, m), 4.59 (2H, d, J = 4.4 Hz), 3.96 (1H, dd, J = 12.7, 2.4 Hz), 3.79 (1H, dd, J = 11.5, 3.0 Hz), 3.67 (1H, dd, J = 12.7, 4.1 Hz), 3.55 (1H, dd, J = 11.6, 5.5 Hz), 3.26 (1H, m), 3.12 (1H, m).

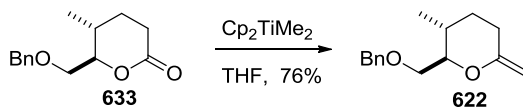


Ester 641. Freshly made carbethoxymethylene triphenylphosphorane (18.18g, 50.2 mmol) and aldehyde **640** (8.86g, 45.6 mmol) were refluxed in benzene (225 mL) over the period of 18 hours. The reaction mixture was cooled to room temperature and concentrated. Purification by flash column chromatography (SiO₂; 8:1, hexanes:ethyl acetate) yielded ester **641** as a single isomer with a yellow oil appearance. The ¹H NMR data of this compound corresponded to that in the literature.⁹⁰ TLC: R_f = 0.31 (10:1, hexanes:EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 7.33 (5H, m), 6.67 (1H, dd, *J* = 15.7, 7.2 Hz), 6.16 (1H, dd, *J* = 15.7, 0.7 Hz), 4.59 (2H, s), 4.21 (2H, q, *J* = 7.1 Hz), 3.77 (1H, dd, *J* = 11.6, 3.2 Hz), 3.59 (1H, dd, *J* = 11.6, 5.0 Hz), 3.44 (1H, dd, *J* = 11.7, 7.2), 3.16 (1H, m), 1.29 (3H, t, *J* = 7.1 Hz).

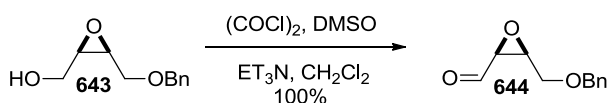


Lactone 622. Alcohol **632** (2.05g, 7.36 mmol) and 10% Pd/C (0.30g, 0.28 mmol) was diluted in methanol (25 mL). The reaction mixture was subjected to hydrogen gas by means of an attached balloon. The reaction was stirred vigorously for 48 h. The reaction mixture was filtered through a pad of celit and washed with a 10% aqueous HCl solution. The organic and aqueous layers were separated. The aqueous layers were subsequently extracted with ethyl acetate (3 x 30 mL). Combined organic layers were dried with MgSO₄, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (SiO₂, 5:1-2:1, hexanes/ethyl acetate) yielded the desired lactone **622** as a colorless oil (1.10g, 64%). TLC: R_f = 0.29 (2:1, hexanes:EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 7.34 (5H, m), 4.59 (2H, dd, *J* = 29.6, 12.1 Hz), 4.07 (1H, m), 3.68 (2H, m), 2.63 (1H, ddd, *J* = 17.9, 6.5, 4.2 Hz), 2.49 (1H, ddd, *J* = 17.7, 10.6, 6.9 Hz), 2.08 (1H,

m), 1.93 (1H, m), 1.56 (1H, m), 1.01 (3H, t, $J = 6.6$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 137.8, 128.3, 127.6 (2), 85.1, 73.5, 69.8, 29.6, 28.7, 27.4, 17.1. IR (film): 3031, 2935, 1733 cm^{-1} .

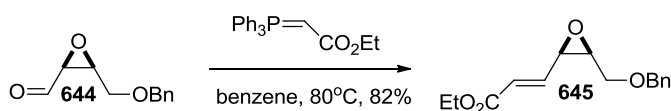


Enol ether 622. To a solution of lactone **633** (0.069g, 0.29 mmol) in 6 mL THF was added Cp_2TiMe_2 (1.17 mL of a 0.5M solution in THF, 0.585 mmol). The resulting mixture was warmed to reflux and stirred for 20 h in the dark. The solution was then cooled to room temperature, concentrated *in vacuo*, and the resulting residue triturated with hexanes. (100 mL). The hexanes solution was filtered through celite and concentrated again. The residue was purified via flash chromatography (SiO_2 ; hexanes:triethylamine, 19:1) to afford the exocyclic enol ether **622** as a yellow oil (0.051 g, 76%). TLC: $R_f = 0.91$ (hexanes: EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 7.34 (5H, m), 4.62 (2H, dd, $J = 35.0, 12.2$ Hz), 4.38 (1H, d, $J = 1.0$), 4.08 (1H, d, $J = 1.3$ Hz), 3.67 (1H, dd, $J = 10.9, 2.7$ Hz), 3.61 (1H, dd, $J = 10.9, 4.4$ Hz), 3.39 (1H, ddd, $J = 9.6, 4.3, 2.7$ Hz), 2.25 (2H, m), 1.85 (2H, m), 1.29 (1H, m), 0.87 (3H, d, $J = 6.5$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 159.3, 138.2, 128.3, 127.6, 127.5, 91.4, 79.7, 73.3, 70.3, 29.4, 29.0, 25.1, 12.7. IR (film): 3010, 3065, 3032, 2956, 2931, 1650 cm^{-1} .

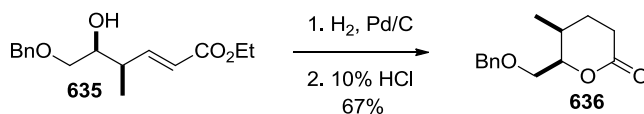


Aldehyde 644. Epoxide **644** (0.50g, 2.57 mmol) was oxidized under Swern conditions using a similar literature procedure.¹⁷ Oxalyl chloride (0.49g, 3.90 mmol) was dissolved in CH_2Cl_2 (13 mL) and cooled to -78°C . DMSO (0.64g, 8.2 mmol) was added dropwise over a period of 15 minutes. The reaction mixture was allowed to stir for an additional 15 minutes until alcohol **643** was added dropwise as a solution in CH_2Cl_2 (1M, 2.6 mL). After stirring for 30 minutes, Et_3N (0.64g, 2.28 mmol) was added dropwise, and the reaction warmed up to room temperature over

the period of an hour. Water was added (100 mL) and the aqueous and organic layers were separated. The aqueous layer was back extracted with CH₂Cl₂ (3 x 80 mL). The organic layers were combined, dried with MgSO₄, filtered, and concentrated to yield product **644** as a yellow oil (0.67g, 100%) which was carried on to the next step without further purification. ¹H NMR data for this compound agreed with the known literature values.⁹¹ TLC: R_f = 0.39 (2:1, hexanes:EtOAc). ¹H NMR (CDCl₃, 300 MHz): 9.45 (1H, d, *J* = 4.8 Hz), 7.34 (5H, m), 4.57 (2H, s), 3.81 (2H, dq, *J* = 11.1, 3.9 Hz), 3.47 (2H, m).

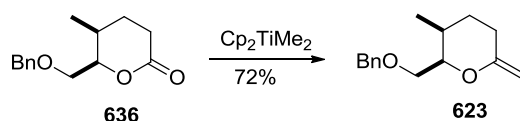


Ester 645. Formation of ester **645** (10.1g, 82%) is achieved by refluxing freshly made carbethoxymethylene triphenylphosphorane (18.7g, 51.5 mmol)¹⁸ in benzene (125 mL) with aldehyde **644** (9.00g, 46.8 mmol) over a period of 18 hours following a similar literature procedure.¹⁷ The reaction mixture is cooled to room temperature and concentrated. The product is purified via flash column chromatography (SiO₂; 8:1, hexanes:ethyl acetate) to yield ester **645** as a yellow oil. ¹H NMR data is consistent with that reported for ester **645**.⁹⁰ TLC: R_f = 0.70 (2:1 hexanes:EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 7.33 (5H, m), 6.77 (1H, dd, *J* = 15.7, 6.6 Hz), 6.15 (1H, dd, *J* = 15.7, 1.0 Hz), 4.58 (2H, dd, *J* = 28.4, 11.9 Hz), 4.21 (2H, q, *J* = 7.1), 3.62 (3H, m), 3.46 (1H, m), 1.31 (3H, t, *J* = 7.1 Hz).

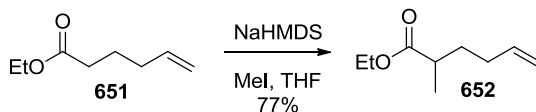


Lactone 636. Hydrogenation of alcohol **635** (1.78g, 6.4 mmol) was accomplished by dilution in methanol (22 mL), along with the addition of 10 % Pd/C (0.30g, 0.28 mmol). The reaction mixture was subjected to hydrogen gas by means of an attached balloon. The reaction was stirred vigorously for 72 h. Filtration through a pad of celite was followed by washing with a

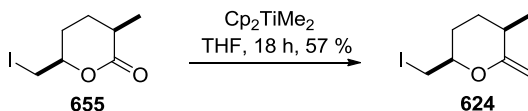
10% aqueous HCl solution. The organic and aqueous layers were separated. Aqueous layers were extracted with ethyl acetate (3 x 30 mL). Combined organic layers were dried with MgSO₄, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (SiO₂, 5:1-2:1, hexanes/ethyl acetate) yielded the desired lactone as a colorless oil (1.00g, 67%). ¹H NMR data corresponds to that of the known lactone.⁹² ¹H NMR (CDCl₃, 300 MHz): δ 7.33 (5H, m), 4.55 (3H, m), 3.64 (2H, ddd, *J* = 24.6, 10.2, 5.5 Hz), 2.56 (2H, dt, *J* = 7.0, 2.4 Hz), 2.23 (1H, m), 2.01 (1H, m), 1.77 (1H, m), 0.97 (3H, d, *J* = 7.1 Hz).



Enol ether 623. To a solution of lactone **636** (0.64g, 2.7 mmol) in 50 mL THF was added Cp₂TiMe₂ (10.9 mL of a 0.5M solution in THF, 5.5 mmol). The resulting mixture was warmed to reflux and stirred for 20 h in the dark. The solution was then cooled to room temperature, concentrated *in vacuo*, and the resulting residue triturated with hexanes. (300 mL). The hexanes solution was filtered through celite and concentrated again. The residue was purified via flash chromatography (SiO₂; hexanes:triethylamine, 19:1) to afford the exocyclic enol ether **623** as a yellow oil (0.44 g, 72%). TLC: R_f = 0.70 (hexanes: EtOAc, 10:1). ¹H NMR (CDCl₃, 300 MHz): δ 7.33 (5H, m), 4.59 (2H, dd, *J* = 33.2, 12.1 Hz), 4.37 (1H, d, *J* = 1.0), 4.09 (1H, d, *J* = 0.9 Hz), 4.00 (1H, m), (1H, dd, *J* = 10.1, 7.0 Hz), 3.48 (1H, dd, *J* = 10.1, 5.1 Hz), 2.33 (1H, m), 2.16 (1H, dt, *J* = 14.4, 5.4 Hz), 1.98 (1H, m), 1.79 (1H, m), 1.56 (1H, m), 0.97 (3H, d, *J* = 7.0 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 159.3 (C), 138.2 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 91.4 (CH₂), 79.7 (CH), 73.3 (CH₂), 70.3 (CH₂), 29.4 (CH₂), 29.0 (CH), 25.1 (CH₂), 12.7 (CH₃). IR (film): 3010, 3065, 3032, 2956, 2931, 1650 cm⁻¹.

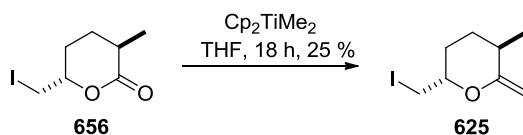


Ester 652. A 1.0 M solution of NaHMDS in THF (9.86 mL, 9.86 mmol) was diluted with THF (15 mL). The reaction was cooled to -78°C and a solution of ester **651** (1.00g, 7.04 mmol) in THF (15 mL) was added dropwise. The reaction mixture was stirred for one hour before addition of MeI (2.19 mL, 35.2 mmol). The reaction was allowed to stir for an additional 3h before quenching at -78°C with glacial acetic acid (4 mL). The reaction mixture was warmed to ambient temperature before adding water (20 mL) and separating the aqueous and organic layers. The aqueous layer was back extracted with EtOAc (3x15 mL). The organic layers were combined, dried with MgSO_4 , filtered, and concentrated. Purification via column chromatography (SiO_2 ; hexanes:EtOAc, 15:1) yielded methylated ester **652** as a yellow oil (0.84 g) in 77% yield. TLC: $R_f = 0.81$ (2:1, hexanes:EtOAc). ^1H NMR (CDCl_3 , 300 MHz): 5.77 (1H, m), 4.99 (2H, m), 4.13 (2H, d, $J = 7.2$ Hz), 2.44 (1H, m), 2.06 (2H, m), 1.76 (1H, m), 1.48 (1H, m), 1.25 (3H, t, $J = 7.1$ Hz), 1.14 (3H, d, $J = 7.0$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 176.7 (C), 137.9 (CH), 115.0 (CH_2), 60.1 (CH_2), 38.9 (CH), 32.8 (CH_2), 31.3 (CH_2), 17.0 (CH_3), 14.2 (CH_3). IR (film): 3079, 2936, 1713, 1641 cm^{-1} .

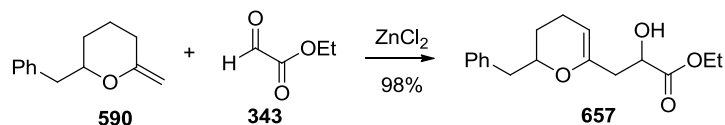


Enol ether 624. To a solution of lactone **655** (0.022 g, 0.087 mmol) in 1.3 mL THF was added Cp_2TiMe_2 (0.38 mL of a 0.5M solution in THF, 0.19 mmol). The resulting mixture was warmed to reflux and stirred for 20 h in the dark. The solution was then cooled to room temperature, concentrated *in vacuo*, and the resulting residue triturated with hexanes. (60 mL). The hexanes solution was filtered through celite and concentrated again. The residue was purified via flash

chromatography (SiO₂; hexanes:triethylamine, 19:1) to afford the exocyclic enol ether **624** as a yellow oil (0.012g, 57%). TLC: R_f = 0.90 (2:1, hexanes:EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 4.43 (1H, s), 4.17 (1H, d, J = 0.5 Hz), 3.84 (1H, m), 3.29 (2H, ddd, J = 17.6, 10.3, 6.1 Hz), 2.39 (1H, m), 1.83 (3H, m), 1.51 (1H, m), 1.14 (3H, d, J = 6.8 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 163.3 (c), 91.3 (CH₂), 76.7 (CH), 32.0 (CH), 28.0 (CH₂), 26.7 (CH₂), 18.7 (CH₃), 8.4 (CH₂). IR (film): 2934, 1647 cm⁻¹.

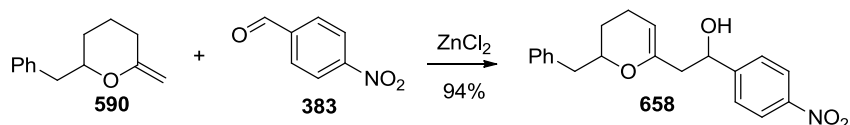


Enol ether 625. To a solution of lactone **656** (0.039 g, 0.153 mmol) in 2.6 mL THF was added Cp₂TiMe₂ (0.61 mL of a 0.5M solution in THF, 0.31 mmol). The resulting mixture was warmed to reflux and stirred for 20 h in the dark. The solution was then cooled to room temperature, concentrated *in vacuo*, and the resulting residue triturated with hexanes. (60 mL). The hexanes solution was filtered through celite and concentrated again. The residue was purified via flash chromatography (SiO₂; hexanes:triethylamine, 19:1) to afford the exocyclic enol ether **625** as a yellow oil (0.010g, 25%). TLC: R_f = 0.89 (2:1, hexanes:EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 4.43 (1H, s), 4.17 (1H, d, J = 0.5 Hz), 3.84 (1H, m), 3.29 (2H, ddd, J = 17.6, 10.3, 6.1 Hz), 2.39 (1H, m), 1.83 (3H, m), 1.51 (1H, m), 1.14 (3H, d, J = 6.8 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 163.3 (C), 91.3 (CH₂), 76.7 (CH), 32.0 (CH), 28.0 (CH₂), 26.7 (CH₂), 18.7 (CH₃), 8.4 (CH₂). IR (film): 2934, 1647 cm⁻¹.



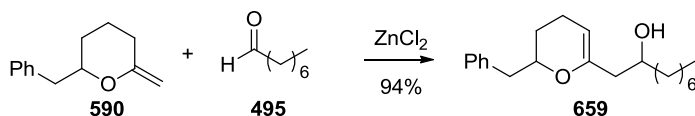
Alcohol 657. Enol ether **590** (0.043 g, 0.23 mmol) was placed into a flame dried flask along with a stir bar and 0.22 mL of THF. Freshly distilled ethyl glyoxylate **343** (0.028 mL, 0.27

mmol) was added to the reaction mixture while stirring. A 0.15 M solution of ZnCl_2 in THF was added (0.08 mL, 0.002 mmol), and the reaction mixture was allowed to stir for two hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2 ; 10:1-6:1, 95% hexanes, 5% $\text{Et}_3\text{N}:\text{EtOAc}$) yielded ene product **657** (0.065 g, 98%), a colorless oil, as a 1.1:1 mixture of diastereomers. TLC: $R_f = 0.39$ (2:1, hexanes:EtOAc). ^1H NMR (CDCl_3 , 300 MHz): δ 7.28 (5H, m), 4.60 (1H, m), 4.21 (3H, m), 4.01 (1H, m), 2.97 (2H, m), 2.79 (1H, m), 2.46 (2H, m), 2.00 (2H, m), 1.81 (1H, m), 1.50 (1H, m), 1.28 (3H, dt, $J = 7.1, 2.5$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 174.1 (C), 149.7 (C), 149.2 (C), 137.8 (C), 129.4 (CH), 129.3 (CH), 128.3 (2) (CH), 126.4 (CH), 126.3 (CH), 98.3 (CH), 98.9 (CH), 98.8 (CH), 76.4 (CH), 76.3 (CH), 69.4 (CH), 68.8 (CH), 61.2 (CH_2), 61.1 (CH_2), 41.6 (CH_2), 41.5 (CH_2), 39.2 (CH_2), 39.1 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 20.3 (CH_2), 20.1 (CH_2), 14.2 (2) (CH_3). IR (film): 3511, 3064, 3028, 2924, 1735, 1680 cm^{-1} .

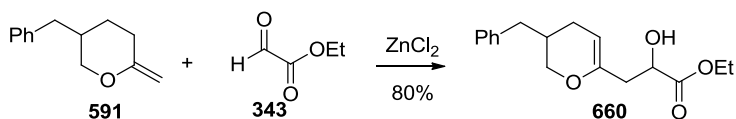


Alcohol 658. Enol ether **590** (0.030g, 0.170) was placed into a flame dried flask along with a stir bar and 0.35 mL of THF. *p*-Nitrobenzaldehyde **383** (0.023g, 0.15 mmol) was added to the reaction mixture while stirring. A 0.1 M solution of ZnCl_2 in THF was added (0.077 mL, 0.0080 mmol), and the reaction mixture was allowed to stir for two hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2 ; 10:1-7:1, 95% hexanes, 5% $\text{Et}_3\text{N}:\text{EtOAc}$) yielded ene product **658** (0.049, 94%), a colorless oil, as a 1:1 mixture of diastereomers. TLC: $R_f = 0.62$ (2:1, hexanes:EtOAc). ^1H NMR (CDCl_3 , 300 MHz): δ 8.15 (2H, m), 7.35 (7H, m), 4.89 (1H, dd, $J=7.8, 4.4$ Hz), 4.55 (0.5H, t, $J=3.5$ Hz), 4.48 (0.5 Hz, t, $J=3.4$ Hz), 4.05 (0.5H, m), 3.89 (0.5H, m), 3.03 (1H, s, br), 2.91 (2H, ddd, $J=26.7, 13.5, 6.2$ Hz), 2.56

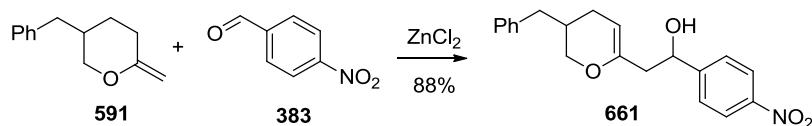
(0.5H, m), 2.35 (1.5H, m), 2.00 (2H, m), 1.86 (1H, m), 1.56 (1H, m). ^{13}C NMR (CDCl_3 , 75 MHz): δ 151.2 (C), 150.3 (C), 150.2 (C), 146.9 (C), 137.9 (C), 137.8 (C), 129.3 (2) (CH), 128.5 (2) (CH), 126.7 (CH), 126.6 (CH), 126.4 (CH), 126.2 (CH), 123.4 (CH), 123.3 (CH), 99.3 (CH), 98.9 (CH), 76.7 (CH), 71.9 (CH), 71.6 (CH), 44.1 (CH_2), 43.4 (CH_2), 41.7 (CH_2), 41.6 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 20.2 (CH_2), 20.2 (CH_2). IR (film): 3339, 3064, 3029, 2920, 1678, 1603, 1520, 1345 cm^{-1} .



Alcohol 659. Enol ether **590** (0.068g, 0.361 mmol) was placed into a flame dried flask along with a stir bar and 0.56 mL of THF. Octyl aldehyde **495** (0.051g, 0.397 mmol) was added to the reaction mixture while stirring. A 0.5 M solution of ZnCl_2 in THF was added (0.143 mL, 0.072 mmol), and the reaction mixture was allowed to stir for 11 hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2 ; 15:1-7:1, 95% hexanes, 5% $\text{Et}_3\text{N}:\text{EtOAc}$) yielded ene product **659** (0.095g, 83%), a colorless oil, as a 1:1 mixture of diastereomers. TLC: R_f = 0.82 (2:1, hexanes:EtOAc). ^1H NMR (CDCl_3 , 300 MHz): δ 7.26 (5H, m), 4.55 (1H, t, J = 3.6 Hz), 4.02 (1H, m), 3.76 (1H, m), 2.60 (2H, dd, J = 7.1, 4.1 Hz), 2.31 (1H, t, J = 3.5 Hz), 2.52 (1H, d, J = 13.8 Hz), 2.08 (3H, m), 1.77 (2H, m), 1.36 (12H, m), 0.89 (3H, t, J = 6.6 Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 151.8 (C), 151.7 (C), 139.7 (C), 129.0 (CH), 128.3 (CH), 126.1 (CH), 97.1 (CH), 70.0 (CH), 69.9 (CH), 69.7 (CH), 69.6 (CH), 41.8 (CH_2), 41.8 (CH_2), 38.2 (2) (CH_2), 36.8 (CH_2), 33.8 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 26.6 (CH_2), 25.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3). IR(film): 3585, 3030, 2926, 2857, 1605 cm^{-1} .

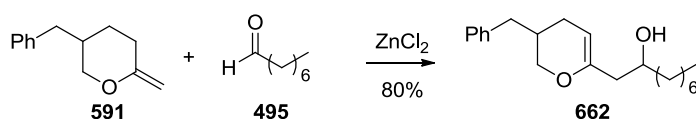


Alcohol 660. Enol ether **591** (0.075g, 0.371) was placed into a flame dried flask along with a stir bar and 0.40 mL of THF. Freshly distilled ethyl glyoxylate **343** (0.049 mL, 0.478 mmol) was added to the reaction mixture while stirring. A 0.15 M solution of ZnCl_2 in THF was added (0.136 mL, 0.020 mmol), and the reaction mixture was allowed to stir for two hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2 ; 10:1-6:1, 95% hexanes, 5% $\text{Et}_3\text{N}:\text{EtOAc}$) yielded ene product **660** (0.085g, 80%) as a colorless oil with a dr of 1:1.3. TLC: $R_f = 0.40$ (2:1, hexanes:EtOAc). ^1H NMR (CDCl_3 , 300 MHz): δ 7.24 (5H, m), 4.59 (1H, ddd, $J = 7.7, 4.0$ Hz), 4.32 (1H, t, $J = 5.3$ Hz), 4.23 (2H, m), 3.96 (1H, m), 3.60 (1H, m), 3.04 (1H, dd, $J = 11.9, 7.3$ Hz), 2.51 (4H, m), 2.08 (2H, m), 1.76 (1H, m), 1.29 (3H, dt, $J = 7.14, 0.4$). ^{13}C NMR (CDCl_3 , 75 MHz): δ 174.2 (C), 174.1 (C), 149.4 (C), 149.1 (C), 139.6 (2) (C), 128.9 (CH), 128.2 (CH), 126.0 (CH), 98.3 (CH), 98.1 (CH), 69.4 (CH_2), 68.9 (CH), 68.6 (CH), 61.3 (2) (CH_2), 39.0 (CH_2), 38.1 (CH_2), 38.0 (CH_2), 33.7 (CH), 33.6 (CH), 26.6 (CH_2), 26.4 (CH_2), 14.1 (CH_3). IR (film): 3324, 3028, 2923, 1735, 1681 cm^{-1} .

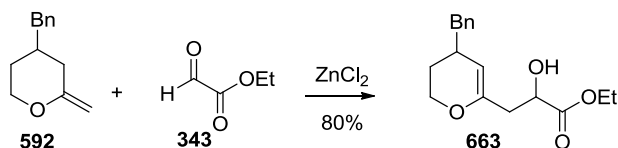


Alcohol 661. Enol ether **591** (0.040 g, 0.22 mmol) was placed into a flame dried flask along with a stir bar and 0.40 mL of THF. *p*-Nitrobenzaldehyde **383** (0.030g, 0.20 mmol) was added to the reaction mixture while stirring. A 0.1 M solution of ZnCl_2 in THF was added (0.10 mL, 0.010 mmol), and the reaction mixture was allowed to stir for two hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2 ; 10:1-7:1, 95% hexanes, 5% $\text{Et}_3\text{N}:\text{EtOAc}$) yielded ene adduct **661** (0.059, 88%), a colorless oil, as a 1.4:1 ratio

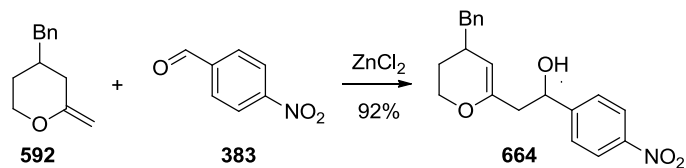
of diastereomers. TLC: $R_f = 0.65$ (2:1, hexanes:EtOAc). ^1H NMR (CDCl_3 , 300 MHz): δ 8.21 (2H, m), 7.54 (2H, m), 7.26 (5H, m), 5.00 (1H, m), 4.57 (1H, m), 4.04 (1H, m), 3.66 (1H, ddd, $J = 13.1, 10.5, 8.3$ Hz), 3.07 (1H, m), 2.60 (2H, m), 2.49 (1H, m), 2.35 (1H, m), 2.10 (2H, m), 1.76 (1H, m). ^{13}C NMR (CDCl_3 , 75 MHz): δ 151.2 (C), 150.3 (C), 147.1 (C), 139.4 (C), 128.9 (CH), 128.4 (CH), 128.3 (CH), 126.4 (2) (CH), 126.2 (CH), 123.5 (CH), 98.6 (CH), 71.7 (CH), 71.6 (CH), 69.9 (CH_2), 69.8 (CH_2), 44.1 (CH_2), 44.0 (CH_2), 38.2 (CH_2), 33.7 (CH), 26.5 (CH_2). IR (film): 3547, 3081, 3026, 2918, 1679, 1603, 1519, 1346 cm^{-1} .



Alcohol 662. Enol ether **591** (0.045g, 0.239 mmol) was placed into a flame dried flask along with a stir bar and 0.18 mL of THF. Octyl aldehyde **495** (0.031g, 0.239 mmol) was added to the reaction mixture while stirring. A 0.16 M solution of ZnCl_2 in THF was added (0.30 mL, 0.048 mmol), and the reaction mixture was allowed to stir for 11 hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2 ; 15:1-7:1, 95% hexanes, 5% Et_3N :EtOAc) yielded ene product **100** (0.060, 80%), a colorless oil, as a 1.3:1 mixture of diastereomers. TLC: $R_f = 0.87$ (2:1, hexanes:EtOAc). ^1H NMR (CDCl_3 , 300 MHz): δ 7.26 (5H, m), 4.55 (1H, t, $J = 3.6$ Hz), 4.02 (1H, m), 3.76 (1H, m), 3.64 (1H, m), 2.60 (2H, dd, $J = 7.1, 4.1$ Hz), 2.31 (1H, t, $J = 3.5$ Hz), 2.52 (1H, d, $J = 13.8$ Hz), 2.08 (3H, m), 1.77 (1H, m), 1.36 (12H, m), 0.89 (3H, t, $J = 6.6$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 151.8 (C), 151.7 (C), 139.7 (C), 129.0 (CH), 128.3 (CH), 126.1 (CH), 97.1 (CH), 70.0 (CH_2), 69.9 (CH_2), 69.7 (CH), 69.6 (CH), 41.8 (CH_2), 41.8 (CH_2), 38.2 (2) (CH_2), 36.8 (CH_2), 33.8 (CH), 31.8 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 26.6 (CH_2), 25.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3). IR (film): 3501, 3028, 2926, 2855, 1678 cm^{-1} .

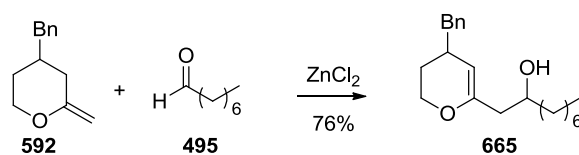


Alcohol 663. Enol ether **592** (0.020 g, 0.11 mmol) was placed into a flame dried flask along with a stir bar and 0.21 mL of THF. Freshly distilled ethyl glyoxylate **343** (0.011 mL, 0.12 mmol) was added to the reaction mixture while stirring. A 0.07 M solution of ZnCl_2 in THF was added (0.08 mL, 0.005 mmol), and the reaction mixture was allowed to stir for two hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2 ; 8:1-5:1, 95% hexanes, 5% $\text{Et}_3\text{N}:\text{EtOAc}$) yielded ene product **663** (0.030 g, 100%) as a colorless oil with a dr of 2.4:1. TLC: $R_f = 0.59$ (2:1, hexanes:EtOAc). ^1H NMR (CDCl_3 , 300 MHz): δ 7.23 (5H, m), 4.54 (1H, d, $J = 2.3$ Hz), 4.32 (1H, m), 4.23 (2H, dq, $J = 7.1, 1.7$ Hz), 4.03 (1H, m), 3.90 (1H, m), 2.97 (1H, dd, $J = 7.3, 2.5$ Hz), 2.54 (5H, m), 1.79 (1H, m), 1.56 (1H, m), (3H, dt, $J = 7.1, 4.6$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 174.1 (C), 149.5 (C), 140.0 (C), 129.0 (CH), 128.3 (CH), 126.0 (CH), 103.8 (CH), 103.7 (CH), 68.9 (CH), 65.0 (CH_2), 64.9 (CH_2), 61.4 (CH_2), 42.8 (CH_2), 39.4 (CH_2), 39.3 (CH_2), 32.8 (CH), 32.7 (CH), 28.3 (CH_2), 28.2 (CH_2), 14.2 (CH_3). IR (film): 3475, 3062, 3027, 2928, 1734, 1674 cm^{-1} .



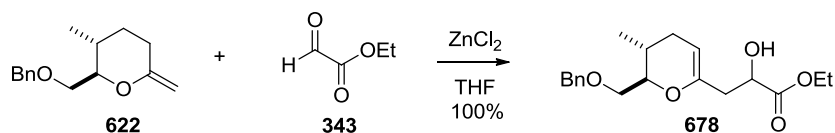
Alcohol 664. Enol ether **592** (0.010g, 0.053) was placed into a flame dried flask along with a stir bar and 0.65 mL of THF. *p*-Nitrobenzaldehyde **383** (0.007g, 0.048 mmol) was added to the reaction mixture while stirring. A 0.1 M solution of ZnCl_2 in THF was added (0.071 mL, 0.0020 mmol), and the reaction mixture was allowed to stir for two hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2 ; 10:1-7:1, 95% hexanes,

5% Et₃N:EtOAc) yielded ene product **664** (0.015, 92%), a colorless oil, as a 2.6:1 ratio of diastereomers. TLC: *R_f* = 0.62 (2:1, hexanes:EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 8.21 (2H, d, *J*=8.8 Hz), 7.53 (2H, d, *J*=8.4 Hz), 7.26 (3H, m), 7.12 (2H, m), 4.98 (1H, m), 4.48 (1H, m), 4.10 (1H, m), 3.95 (1H, m), 3.07 (0.19H, s), 3.00 (0.81H, s), 2.58 (2H, m), 2.47 (2H, m), 2.33 (1H, m), 1.82 (1H, m), 1.56 (1H, m). ¹³C NMR (CDCl₃, 75 MHz): δ 151.2 (C), 150.3 (C), 147.1 (C), 139.7 (C), 139.6 (C), 129.0 (CH), 128.3 (CH), 126.4 (CH), 126.1 (CH), 123.5 (CH), 103.9 (2) (CH), 71.6 (CH), 71.6 (CH), 65.2 (CH₂), 65.1 (CH₂), 44.4 (CH₂), 44.3 (CH₂), 42.7 (CH₂), 32.6 (CH), 32.5 (CH), 28.3 (CH₂), 28.2 (CH₂). IR (film): 3498, 3027, 2923, 1673, 1603, 1520, 1346 cm⁻¹.

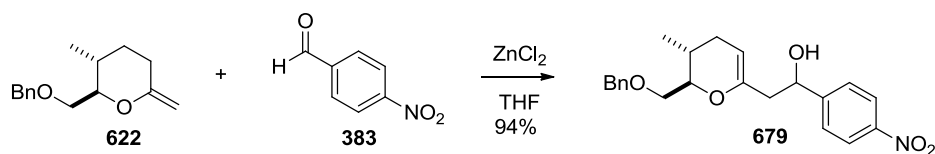


Alcohol 665. Enol ether **592** (0.022g, 0.117) was placed into a flame dried flask along with a stir bar and 0.11 mL of THF. Octyl aldehyde **495** (0.016g, 0.129 mmol) was added to the reaction mixture while stirring. A 0.73 M solution of ZnCl₂ in THF was added (0.03 mL, 0.023 mmol), and the reaction mixture was allowed to stir for 11 hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO₂; 20:1-10:1, 95% hexanes, 5% Et₃N:EtOAc) yielded ene product **665** (0.028, 76%), a colorless oil, as a 2.4:1 ratio of diastereomers. TLC: *R_f* = 0.81 (2:1, hexanes:EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 7.24 (5H, m), 4.50 (1H, s), 4.06 (1H, m), 3.94 (1H, m), 3.74 (1H, m), 2.57 (2H, m), 2.30 (2H, m), 2.04 (1H, m), 1.80 (1H, m), 1.37 (13H, m), 0.89 (3H, t, *J* = 6.6 Hz) ¹³C NMR (CDCl₃, 75 MHz): δ 151.8 (C), 140.0 (C), 129.0 (CH), 128.3 (CH), 126.0 (CH), 102.7 (CH), 69.6 (CH), 65.0 (CH₂), 64.9 (CH₂), 43.0 (CH₂), 42.9 (CH₂), 42.1 (CH₂), 42.0 (CH₂), 36.8 (CH₂), 32.7 (CH₂), 31.8 (CH),

29.6 (CH₂), 29.3 (CH₂), 28.4 (CH₂), 25.7 (CH₂), 22.7 (CH₂), 14.1 (CH₃) IR (film): 3028, 2928, 1670, 1603 cm⁻¹.

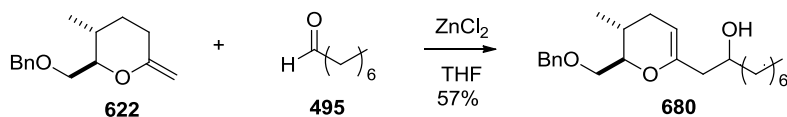


Alcohol 678. Enol ether **622** (0.023 g, 0.10 mmol) was placed into a flame dried flask along with a stir bar and 0.20 mL of THF. Freshly distilled ethyl glyoxylate **343** (0.012 mL, 0.12 mmol) was added to the reaction mixture while stirring. A 0.15 M solution of ZnCl₂ in THF was added (0.03 mL, 0.004 mmol), and the reaction mixture was allowed to stir for two hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO₂; 9:1-5:1, 95% hexanes, 5% Et₃N:EtOAc) yielded ene adduct **678** (0.033 g, 100%) as a colorless oil with a dr of 1.3:1. TLC: R_f = 0.54 (2:1, hexanes:EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 7.32 (5H, m), 4.61 (3H, m), 4.35 (1H, m), 4.21 (2H, m), 3.65 (3H, m), 3.25 (1H, ddd, *J* = 11.6, 7.5 Hz), 2.50 (2H, m), 2.05 (1H, dt, *J* = 16.6, 5.0), 1.91 (1H, m), 1.70 (1H, m), 1.28 (3H, dt, *J* = 7.1, 1.5 Hz), 0.95 (3H, dd, *J* = 6.6, 4.4 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 174.1 (C), 149.1 (C), 148.4 (C), 138.1 (C), 128.3 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 98.3 (2) (CH), 79.8 (CH), 79.5 (CH), 73.3 (CH₂), 70.2 (CH₂), 70.1 (CH₂), 69.4 (CH), 69.0 (CH), 61.2 (2) (CH₂), 38.9 (CH₂), 28.4 (CH), 28.0 (CH), 27.6 (CH₂), 27.3 (CH₂), 17.6 (CH₃), 17.4 (CH₃), 14.2 (CH₃). IR (film): 3496, 3065, 3031, 2959, 1736, 1683 cm⁻¹.



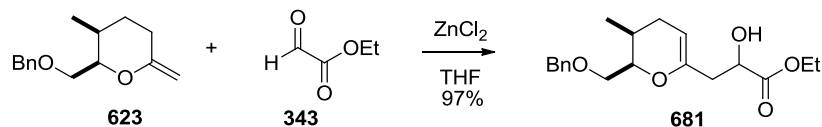
Alcohol 679. Enol ether **622** (0.015 g, 0.065 mmol) was placed into a flame dried flask along with a stir bar and 0.21 mL of THF. *p*-Nitrobenzaldehyde **383** (0.008 g, 0.054 mmol) was added to the reaction mixture while stirring. A 0.18 M solution of ZnCl₂ in THF was added (0.015 mL,

0.003 mmol), and the reaction mixture was allowed to stir for two hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO₂; 10:1-8:1, 95% hexanes, 5% Et₃N:EtOAc) yielded ene adduct **679** (0.019 g, 94%), a colorless oil, as a 1.4:1 ratio of diastereomers. TLC: R_f = 0.55 (2:1, hexanes:EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 8.18 (2H, dd, J = 8.9, 2.2 Hz), 7.54 (2H, d, J = 7.8 Hz), 7.34 (5H, m), 5.01 (1H, m), 4.61 (2H, dd, J = 16.4, 12.3 Hz), 4.52 (1H, dd, J = 4.4, 2.9 Hz), 3.66 (3H, m), 3.54 (1H, br s), 2.54 (1H, dd, J = 14.2, 2.9 Hz), 2.37 (1H, m), 2.02 (1H, dt, J = 16.6, 5.1 Hz), 1.89 (1H, m), 1.67 (1H, m), 0.95 (3H, t, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 151.4 (C), 149.7 (C), 149.3 (C), 147.0 (C), 137.9 (C), 128.4 (CH), 127.7 (CH), 126.5 (CH), 123.4 (CH), 98.4 (CH), 79.9 (CH), 79.6 (CH), 73.5 (CH₂), 73.4 (CH₂), 72.1 (CH), 71.7 (CH), 70.1 (CH₂), 70.0 (CH₂), 43.6 (CH₂), 43.5 (CH₂), 28.2 (CH₂), 28.0 (CH₂), 27.5 (2) (CH), 17.5 (CH₃), 17.4 (CH₃). IR (film): 3503, 3124, 3066, 2915, 1682, 1603, 1519, 1346 cm⁻¹.

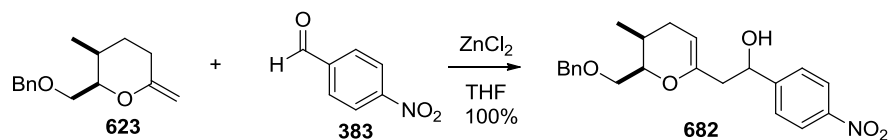


Alcohol 680. Enol ether **622** (0.0230g, 0.09980) was placed into a flame dried flask along with a stir bar and 0.20 mL of THF. Octyl aldehyde **495** (0.0110g, 0.083 mmol) was added to the reaction mixture while stirring. A 0.13 M solution of ZnCl₂ in THF was added (0.126 mL, 0.0166 mmol), and the reaction mixture was allowed to stir for eleven hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO₂; 20:1-5:1, 95% hexanes, 5% Et₃N:ethyl acetate) yielded ene product **680** (0.0171g, 57%), a colorless oil as a mixture of diastereomers. TLC: R_f = 0.84 (2:1, hexanes:EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 7.32 (5H, m), 4.58 (3H, m), 3.63 (2H, d, J = 4.1 Hz), 3.72 (2H, m), 2.67 (1H, dd, J = 35.9, 3.4 Hz), 2.28 (1H, d, J = 14.1 Hz), 2.07 (2H, m), 1.92 (1H, m), 1.70 (1H, m), 1.33 (12H, m), 0.92

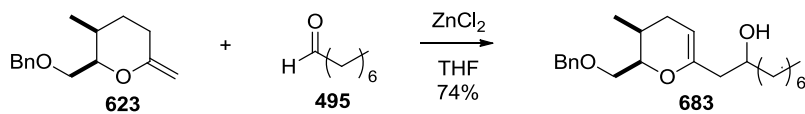
(6H, m). ^{13}C NMR (CDCl_3 , 75 MHz): δ 151.2 (C), 150.9 (C), 128.4 (CH), 127.7 (CH), 127.6 (CH), 97.1 (CH), 97.0 (CH), 79.7 (CH), 79.5 (CH), 73.4 (2) (CH_2), 70.3 (CH), 70.3 (CH_2), 70.0 (CH), 41.6 (2) (CH_2), 36.8 (2) (CH_2), 36.6 (CH_2), 31.8 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 27.6 (CH), 25.8 (CH_2), 22.7 (CH_2), 17.6 (CH_3), 17.5 (CH_3), 14.1 (CH_3). IR (film): 3528, 3033, 2956, 1681, 1603 cm^{-1} .



Alcohol 681. Enol ether **623** (0.0230g, 0.0998) was placed into a flame dried flask along with a stir bar and 0.20 mL of THF. Freshly distilled ethyl glyoxylate **343** (0.0122 mL, 0.120 mmol) was added to the reaction mixture while stirring. A 0.15 M solution of ZnCl_2 in THF was added (0.0300 mL, 0.00415 mmol), and the reaction mixture was allowed to stir for two hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2 ; 10:1-5:1, 95% hexanes, 5% Et_3N :ethyl acetate) yielded ene product **681** (0.0320g, 97%) as a colorless oil with a dr of 2.6:1. TLC: R_f = 0.47 (2:1, hexanes:EtOAc). ^1H NMR (CDCl_3 , 300 MHz): δ 7.33 (5H, m), 4.60 (3H, m), 4.36 (1H, m), 4.21 (2H, dq, J = 7.2, 2.3 Hz), 4.12 (1H, m), 3.62 (1H, m), 3.46 (1H, m), 3.39 (1H, d, J = 8.0 Hz), 2.38 (3H, m), 2.05 (1H, m), 1.64 (1H, m), 1.28 (3H, t, J = 7.1 Hz), 0.89 (3H, dd, J = 7.0, 2.1 Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 174.0 (C), 148.0 (C), 138.0 (C), 128.4 (CH), 127.8 (CH), 127.7 (2) (CH), 97.9 (CH), 97.7 (CH), 76.9 (CH), 73.3 (CH_2), 73.2 (CH_2), 69.8 (CH_2), 69.3 (CH), 69.2 (CH), 68.7 (CH_2), 61.3 (CH_2), 61.2 (CH_2), 38.8 (CH_2), 28.4 (CH_2), 27.9 (CH_2), 27.3 (CH), 27.1 (CH_3), 14.2 (CH_3). IR (film): 3473, 3066, 2924, 1735, 1676 cm^{-1} .

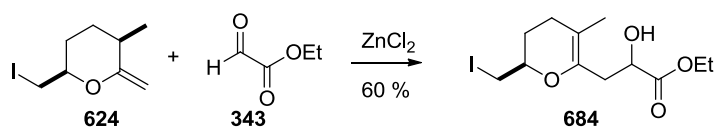


Alcohol 682. Enol ether **623** (0.0230g, 0.0998) was placed into a flame dried flask along with a stir bar and 0.20 mL of THF. *p*-Nitrobenzaldehyde **383** (0.0120g, 0.084 mmol) was added to the reaction mixture while stirring. A 0.18 M solution of ZnCl_2 in THF was added (0.0233 mL, 0.0040 mmol), and the reaction mixture was allowed to stir for two hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2 ; 10:1-5:1, 95% hexanes, 5% Et_3N :ethyl acetate) yielded ene product **682** (0.0300g, 100%) as a colorless oil with a dr of 3.5:1. TLC: R_f = 0.47 (2:1, hexanes:EtOAc). ^1H NMR (CDCl_3 , 300 MHz): δ 8.19 (2H, d, J = 8.8 Hz), 7.54 (2H, d, J = 8.3 Hz), 7.24 (5H, m), 5.01 (1H, m), 4.56 (3H, m), 4.14 (1H, m), 3.66 (1H, m), 3.48 (1H, dd, J = 10.2, 4.0 Hz), 2.30 (4H, m), 1.66 (1H, m), 0.88 (3H, d, J = 6.9 Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 151.5 (C), 148.9 (C), 147.0 (C), 137.7 (C), 128.5 (CH), 128.3 (CH), 127.8 (2) (CH), 126.4 (CH), 123.5 (CH), 98.2 (CH), 77.2 (CH), 79.9 (CH), 73.3 (CH₂), 71.2 (CH), 69.0 (CH₂), 43.7 (CH₂), 28.0 (CH₂), 27.5 (CH), 14.3 (CH₃). IR (film): 3421, 3066, 2964, 1603, 1519, 1345 cm^{-1} .

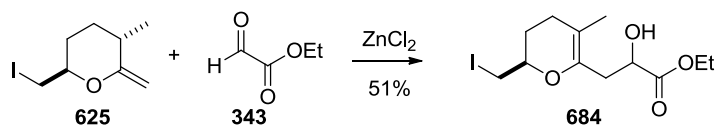


Alcohol 683. Enol ether **623** (0.0180g, 0.0770) was placed into a flame dried flask along with a stir bar and 0.15 mL of THF. Octyl aldehyde **495** (0.0090g, 0.0640 mmol) was added to the reaction mixture while stirring. A 0.18 M solution of ZnCl_2 in THF was added (0.0184 mL, 0.0030 mmol), and the reaction mixture was allowed to stir for eleven hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2 ; 10:1-5:1, 95% hexanes, 5% Et_3N :ethyl acetate) yielded ene product **683** (0.017g, 74%) as a colorless oil

with a 1.7:1 mixture of diastereomers. TLC: R_f = 0.69 (2:1, hexanes:EtOAc). ^1H NMR (CDCl_3 , 300 MHz): δ 7.32 (5H, m), 4.57 (3H, m), 4.13 (1H, m), 3.78 (1H, m), 3.63 (1H, m), 3.48 (1H, m), 2.68 (1H, br s), 2.27 (2H, m), 2.07 (2H, m), 1.68 (1H, m), 1.23 (12H, m), 1.04 (3H, t, J =7.2 Hz), 0.93 (3H, m). ^{13}C NMR (CDCl_3 , 75 MHz): δ 150.8 (C), 150.3 (C), 138.0 (C), 137.9 (C), 128.4 (CH), 127.7 (3) (CH), 96.7 (CH), 96.5 (CH), 76.8 (CH), 73.4 (CH_2), 73.3 (CH_2), 70.6 (CH), 69.7 (CH), 69.4 (CH_2), 69.2 (CH_2), 41.6 (2) (CH_2), 36.8 (2) (CH_2), 31.8 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 27.4 (CH), 27.3 (CH), 25.7 (CH_2), 22.7 (CH_2), 14.2 (CH_2), (CH_3) 14.1 (CH_3), 13.8 (CH_3). IR (film): 3498, 3032, 2927, 2856, 1677 cm^{-1} .



Alcohol 684. Enol ether **624** (0.030g, 0.119 mmol) was placed into a flame dried flask along with a stir bar and 0.238 mL of THF. Freshly distilled ethyl glyoxylate **343** (0.013 mL, 0.131 mmol) was added to the reaction mixture while stirring. A 0.10 M solution of ZnCl_2 in THF was added (0.06 mL, 0.006 mmol), and the reaction mixture was allowed to stir for two hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2 ; 10:1-5:1, 95% hexanes, 5% Et_3N :ethyl acetate) yielded the colorless oil ene product **684** (0.025g, 60%) as a 1:2 mixture of diastereomers. TLC: R_f = 0.51 (2:1, hexanes:EtOAc). ^1H NMR (CDCl_3 , 300 MHz): δ 4.39 (1H, m), 4.22 (2H, m), 3.78 (0.33H, m), 3.67 (0.67H, m), 3.25 (2H, m), 3.18 (0.33H, d, J = 7.9 Hz), 3.00 (0.66H, d, J = 7.2 Hz), 2.64 (2H, m), 2.02 (3H, m), 1.71 (1H, m), 1.61 (3H, s), 1.30 (3H, dt, J = 7.1, 1.6 Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 174.4 (C), 142.8 (C), 105.8 (C), 74.3 (CH), 73.4 (CH), 69.6 (CH), 69.3 (CH), 61.3 (CH_2), 34.7 (2) (CH_2), 27.8 (2) (CH_2), 26.4 (CH_2), 26.2 (CH_2), 17.5 (CH_3), 14.2 (CH_3), 8.7 (CH_2), 8.2 (CH_2). IR (film): 3610, 2981, 2923, 1734, 1689 cm^{-1} .



Alcohol 684. Enol ether **625** (0.007g, 0.039 mmol) was placed into a flame dried flask along with a stir bar and 0.078 mL of THF. Freshly distilled ethyl glyoxylate **343** (0.004 mL, 0.044 mmol) was added to the reaction mixture while stirring. A 0.065 M solution of ZnCl₂ in THF was added (0.03 mL, 0.002 mmol), and the reaction mixture was allowed to stir for two hours. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO₂; 10:1-5:1, 95% hexanes, 5% Et₃N:ethyl acetate) yielded the colorless oil ene product **684** (0.005g, 51%) as a 2:1 mixture of diastereomers. TLC: R_f = 0.51 (2:1, hexanes:EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 4.39 (1H, m), 4.22 (2H, m), 3.78 (0.67H, m), 3.67 (0.33H, m), 3.25 (2H, m), 3.18 (0.67H, d, *J* = 7.9 Hz), 3.00 (0.33H, d, *J* = 7.2 Hz), 2.64 (2H, m), 2.02 (3H, m), 1.71 (1H, m), 1.61 (3H, s), 1.30 (3H, dt, *J* = 7.1, 1.6 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 174.4 (C), 142.8 (C), 105.8 (C), 74.3 (CH), 73.4 (CH), 69.6 (CH), 69.3 (CH), 61.3 (CH₂), 34.7 (2) (CH₂), 27.8 (2) (CH₂), 26.4 (CH₂), 26.2 (CH₂), 17.5 (CH₃), 14.2 (CH₃), 8.7 (CH₂), 8.2 (CH₂). IR (film): 3610, 2981, 2923, 1734, 1689 cm⁻¹.

3.6 References

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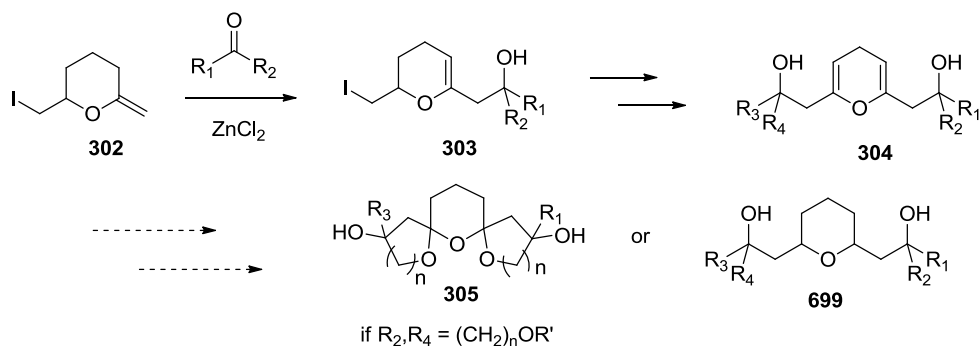
Chapter 4: Formation of Pyrans and Trioxadispiroketal via a Bi-Directional Carbonyl-Ene Approach

4.1 Overview

In light of the recent research concerning the formation of dihydropyranyl ketides via carbonyl-ene reactions of 2-methylenetetrahydropyrans, our focus shifted towards determining the efficacy of a bi-directional approach toward pyran and subsequently trioxadispiroketal synthesis. Such 2,6- β -hydroxypyran may be utilized as advanced synthetic intermediates for natural product synthesis, namely complex trioxadispiroketal systems. This chapter will review trioxadispiroketal including those natural products, which contain such moieties, the chemical aspects of spiroketal systems, previous approaches to trioxadispiroketal synthesis, and our route toward their synthesis.

Herein is described a novel route toward the manufacture of 2,6- β -hydroxypyran via two successive carbonyl-ene reactions (Scheme 4.1). 6-Iodomethylene-2-methylenetetrahydropyran **302** is coupled with enophiles to yield β -hydroxydihydropyrans **303**. Subsequent dehydrohalogenation and secondary coupling of the newly formed 2-methylenedihydropyran to an activated aldehyde yields substituted bis- β -hydroxypyran **304**. The use of these pyran intermediates as bis-spiroketal precursors is also discussed.

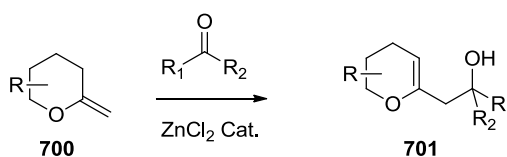
Scheme 4.1



4.2 Background and Significance

Tetrahydropyran and spiroketal functionalities are prevalent in many biologically active natural products, and for this reason their construction is of particular interest to synthetic organic chemists. This current work focuses on the synthesis of 2,6-substituted pyranyl ketides and trioxadispiroketal using our recently discovered carbonyl-ene chemistry of 2-methylene-tetrahydropyrans (Scheme 4.2) via a bi-directional approach. The pyranyl ketides produced (Scheme 4.1) have potential as synthetic precursors to tetrahydropyranyl ketides and spiroketals via reduction or acid-catalyzed ketalization, respectively.

Scheme 4.2



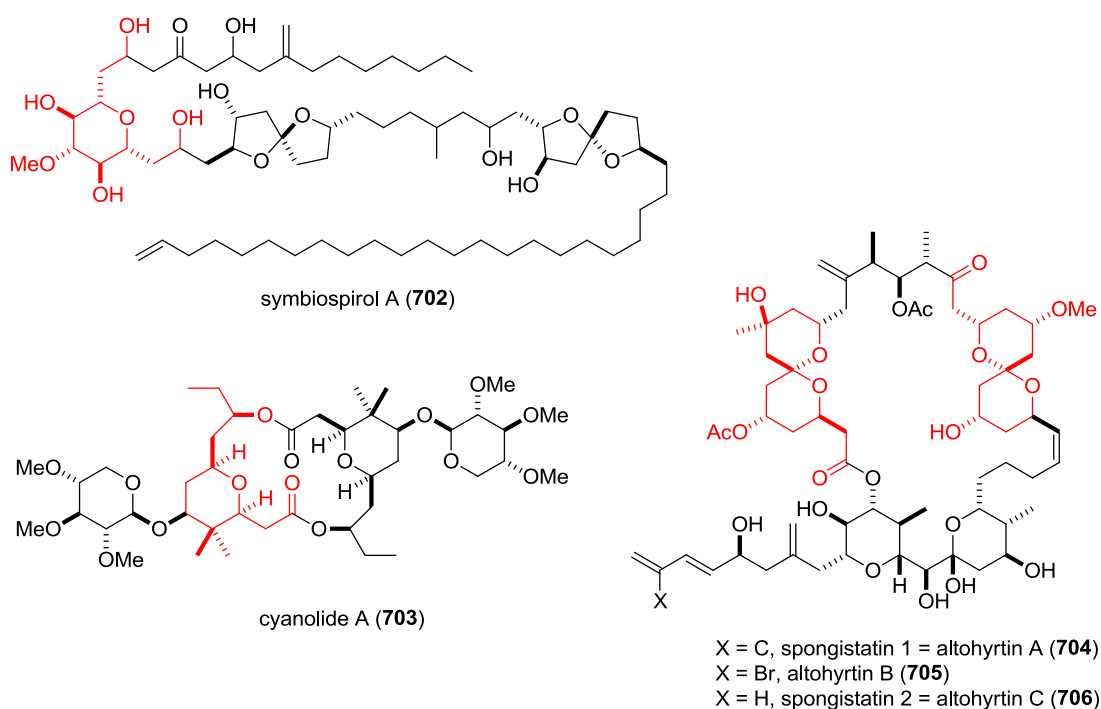
The importance that bis-β-oxygenated tetrahydropyran and trioxadispiroketal moieties have in chemistry is demonstrated by their existence in medically significant, biologically active, natural products. Trioxadispiroketal are especially interesting to synthetic chemists because of their complexity. Anomeric effects, hydrogen bonding, and chelation can all play a role in their stereochemical outcome. Many organic synthetic groups have devised syntheses towards natural products containing complex trioxadispiroketal. Interest in spiroketals and trioxadispiroketal systems has even sparked enough interest to warrant the publication of reviews pertaining to them.¹ This portion of the chapter will examine these topics in detail while also reviewing initial studies toward spiroketal synthesis from exo enol ethers via a carbonyl-ene approach.

Bis-β-Hydroxy-Tetrahydropyran and Trioxadispiroketal-Containing Natural Products

Natural products that contain tetrahydropyranyl ketides, spiroketals or a combination of the two are popular synthetic targets both due to their structural challenge and interesting

biological activities. Symbiospirol A, cyanolide A, and the spongistatins (Figure 4.1) all contain a bis- β -oxygenated tetrahydropyran which could theoretically be constructed through carbonyl ene chemistry.

Figure 4.1



Symbiospirol A (702) was isolated from cultured symbiotic dinoflagellate *Symbiodinium* sp., a single-celled algae, collected from the marine flatworm *Amphiscolops* sp. off the shore of Okinawa, Japan.² Interest in this natural product stems from its demonstrated PKC inhibition, which lends to its potential as an inflammation-suppression drug. The structure of symbiospirol was elucidated, and some of its relative stereochemistry was determined. However, a portion of the relative and absolute stereochemistry has yet to be resolved. Symbiospirol (702) is a 67-linear carbon chain compound that contains a 2,6- β,β' -dihydroxy tetrahydropyran ring.

Cyanolide A (703) was recently isolated from *Lyngbya bouillonii*, a cyanobacterium native to coral off of Papua New Guinea.³ Cyanolide A (703) is a dimeric, 16-membered

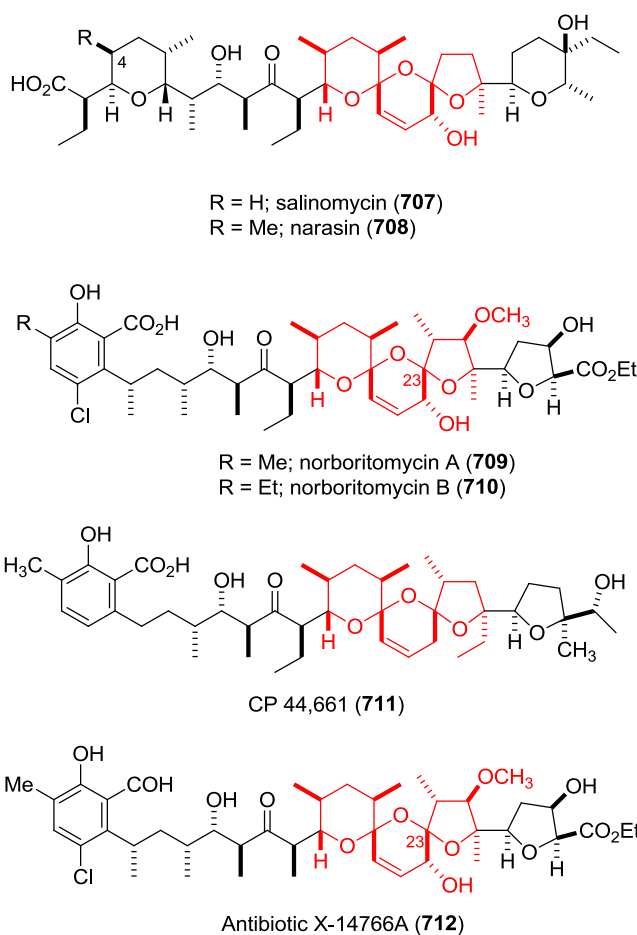
macrocycle that contains two bis- β -oxygenated tetrahydropyrans and two pendant xylose residues. Cyanolide A (**703**) has proven to be a molluscicidal agent against *Biomphalaria glabrata*, a snail that carries the parasites responsible for schistosomiasis infection. Roughly 200 million people are currently infected, making schistosomiasis one of the most prevalent worldwide parasitic infections. By eradicating the parasite at the point of snail infection, the reproductive cycle will halt, effectively eliminating parasitic transmission to humans. The absolute configuration was tentatively assigned based on the natural D-configuration of the xylose residues and was recently confirmed by total synthesis.⁴

The spongistatins (**704**, **705**, **706**) were isolated from several marine sponges and identified by the Pettit and Kobayashi groups concurrently.^{5,6} These compounds show potent cytotoxic effects. The highly substituted macrocyclic lactone consists of two β -keto-(6,6)-spiroketals along with a bis-tetrahydropyranyl unit. Absolute configuration of this complex molecule was finally determined after total synthesis of spongistatin 1 by the Evans group.⁷

Spongistatin 1 has shown the highest toxicity toward cancer cell lines including L1210 murine leukemia cells with IC₅₀ values of 20 pM., kangaroo rat kidney PtK1 cells, possessing IC₅₀ values of 3.6 μ M, and has shown inhibition toward the glutamate-induced polymerization of purified tubulin (IC₅₀ values of 3.6 μ M).⁸ Thus spongistatin 1 shows similar or more potent toxicity than known antimitotic agents such as colchicines, dolastatin 10, vinblastine, and halichondrin B. Use of spongistatin to treat leukemia cell lines has proven to be more effective against long-term survival of cancer cells than 8 out of 10 clinically used cytotoxic drugs due to its XIAP degradation effects.⁹ Spongistatin 1 also acts as a mitosis and microtubule assembly inhibitor. By binding to tubulin, spongistatin 1 prevents cell growth by blocking tubulin receptor sites toward GTP and vinblastine.

Examples of trioxadispiroketal are more limited, but many of the natural products containing these functional groups are bioactive and include examples such as salinomycin, spirolide A, pinnatoxin A, spirastrellolide A and their derivatives (Figures 4.2-4.4). The salinomycin family of natural products, salinomycin (**707**) narasin (**708**), norboritomycin A and B (**709**, **710**), CP 44,661 (**711**), and antibiotic X-14766A (**712**), are all examples of bioactive (6,6,5)-trioxadispiroketal units (Figure 4.2). Isolated from *Streptomyces albus*, salinomycin (**707**)

Figure 4.2



contains a (6,6,5)-trioxaspirodiketal at its core and two pendant, functionalized tetrahydropyranyl rings. This natural product acts as a potent anticoccidial, and as such has been

marketed by Procoxacin as an antibacterial and coccidiostat within the poultry industry to improve overall animal health and production.¹⁰

Narasin (**708**) only differs from salinomycin by the presence of a C₄ methyl group. The alteration in structure is slight and as such Narasin effectively has the same properties as Salinomycin. This natural product is marketed by Elanco animal health as Monteban 45® and is likewise used as a coccidiostat in chickens.

Norboritomycins A and B (**709**, **710**), CP 44,161 (**711**), and antibiotic X-14766A (**712**) are all similar in core structure to salinomycin (**707**), but differ in that a salicylic acid chromophore and tetrahydrofuran ring reside off the trioxadispiroketal. The norboritomycins were isolated from *streptomyces noboritoensis* and their absolute configuration was determined by X-ray crystallography.¹¹ The norboritomycins exhibit biological activity against gram-positive bacteria and *Eimeria teriella* (chicken coccidiosis).

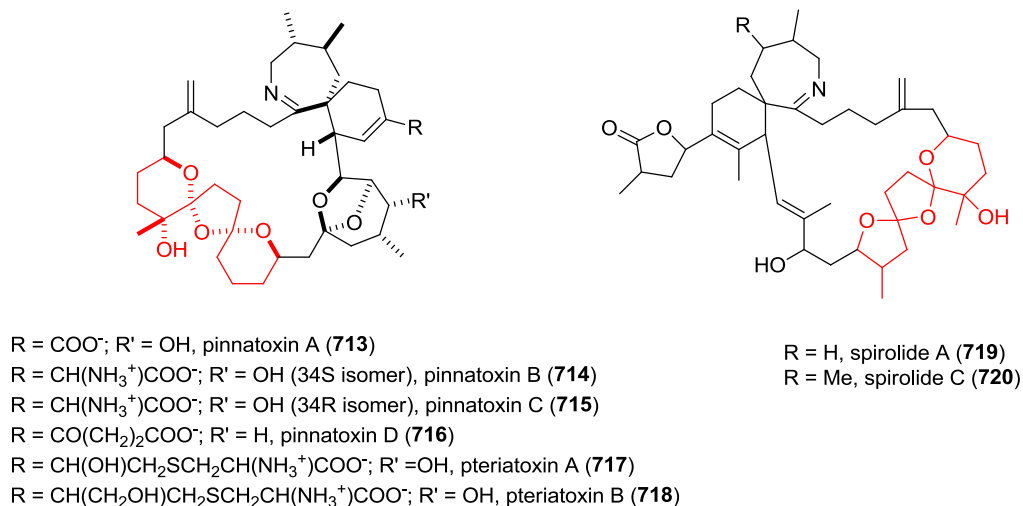
CP 44,161 (**711**) is produced from *Dactylosporangium*, and was isolated in 1978.¹² Much like the properties of the other members of the salinomycin family of natural products, CP 44,161 is a polyether antibiotic with coccidiostat properties. Furthermore this compound has demonstrated broad anti-viral activities against the varicella zoster and herpes viruses.¹³

Antibiotic X-14766A (**712**) was isolated from a fermented culture of *streptomyces malachitofuscus* subsp. *Downeyi*, which is a soil organism native to North America.¹⁴ This natural product demonstrates wide application in agriculture with activities against gram-positive bacteria and protzoa. This compound can be administered in many ways to treat swine dysentery and ketosis or to increase feed utilization in ruminants or swine. Many members within the salinomycin family of natural products are medically significant even with their

diverse sidechains and functionality. This fact lends argument to the importance of the trioxadispiroketal as a key component towards their bioactivity.

The pinnatoxins (**713-716**), pteriatoxins (**717, 718**), and spirolides (**719, 720**) all possess very similar, potent toxicity (Figure 4.3). All three types of natural products were isolated from

Figure 4.3

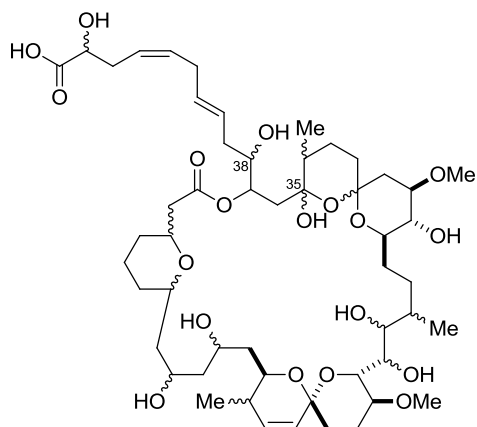


Okinawain shellfish, *Pinna attenuata*,¹⁵ *Petria penguin*,¹⁶ and *Mytilus edulis* and *Placopecten magellanicus*,¹⁷ respectively. These natural products are Ca²⁺ channel activators, and are one of the principal causes for food poisoning resulting from shellfish ingestion. The pinnatoxins have additionally demonstrated cytotoxicity against murine leukemia cell lines.¹⁸ Both their high toxicity and interesting structure are cause for organic synthetic interest.

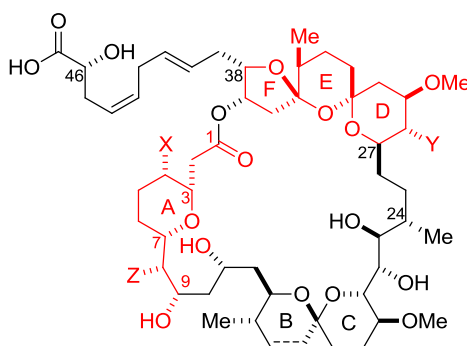
The pinnatoxins and pteriatoxins are very similar structurally, containing a 20-membered macrocyclic core which possesses 14 chiral centers, a (6,5,6)-trioxaspirodiketal, and 5,6 bicyclo-, and 6,7-azaspiro-rings. The pteriatoxins **717** and **718** differ only in that they contain a sulfide side chain. The spirolides also exist as a 20-membered macrocycle, but rather contain a (5,5,6)-bis-spiroketal core.

Of recent interest to many research groups, are efforts toward the synthesis of the spirastrellolides (Figure 4.4). Spirastrellolide A (**721**) was isolated in 2003 from the Caribbean

Figure 4.4



spirastrellolide A, first reported structure (**721**)



X=Z=H, Y=Cl, $\Delta^{15,16}$ spirastrellolide A, revised structure (**376**)

X=Y=Z=H, spirastrellolide B (**722**)

X=Y=H, Z=OH, spirastrellolide C (**723**)

Z=H, X=Y=Cl, spirastrellolide D, $\Delta^{15,16}$ (**724**)

X=Y=Z=H, spirastrellolide E, $\Delta^{15,16}$ (**725**)

X=Z=H, Y=Cl, spirastrellolide F (**726**)

X=Z=H, Y=Cl, $\Delta^{15,16}$ (OMe at C-46), spirastrellolide G (**727**)

marine sponge *Spirastrella coccinea*, after which structure revision and comparison to a spirastrellolide B analog led to elucidation of the absolute configuration (**376**).¹⁹ Spirastrellolide A is a 38-membered macrolide that possesses 21 stereocenters, a *cis*-fused tetrahydropyran ring (A), a [6,6]-spiroketal (BC rings), a [5,6,6]-bis spiroketal (DEF rings), and a skipped-(*E/Z*)-diene side chain. Synthetic interest is based not only on spirastrellolide's complex structure, but also on its interesting biological activity.

Spirastrellolide A (**376**) has been demonstrated to be a potent and selective inhibitor of Ser/Thr protein phosphatase 2A. This activity causes cells to prematurely enter into mitosis, leading to cell death, and thus spirastrellolide A has potential as an anticancer agent or as a treatment for neurological disorders. Clinical development of spirastrellolide A (**376**) could therefore act as an alternative to cancer treatments like Taxol[®], which effect tubulin

polymerization. Full clinical testing of spirastrellolide is currently problematic due to the low yield of isolated material from natural sources.

The structure of spirastrellolide A published initially lacked the F-ring of the trioxadispiroketal moiety, the C₂₈ chlorine, and much of the relative stereochemistry found in the compound. Work published in 2004 demonstrated the presence of the trioxadispiroketal moiety in spirastrellolide A, after acetylation of a methyl ester derivative did not result in incorporation at the C₃₅ or C₃₈ alcohols in proposed structure **721**. Much of the relative stereochemistry was also determined at this time, along with the discovery of the C₂₈ chloro substituent. Relative configurations were determined within three segments (C₃-C₇, C₉-C₂₄, and C₂₇-C₃₈), however, the stereochemical relationships between segments, the configuration of the C₄₆ stereocenter, and the absolute stereochemistry were not discovered until additional analysis of spirastrellolide B furnished further insight.

Spirastrellolide B (**722**), isolated in 2007, has been instrumental in determining the absolute configuration of the macrolide core. X-ray diffraction analysis of the methyl ester derivative of compound **722** yielded the absolute stereochemistry of this compound. Since the NMR data of spirastrellolide B closely resembled that of A, it was deduced that the absolute stereochemistry was the same for both isomers. Shortly thereafter five other spirastrellolide macrolides (C-G) were isolated and identified from the same sponge.²⁰ The main structural difference between the spirastrellolide members is the presence or absence of chlorine at C₄ and C₂₈, and the presence or absence of an olefin within the B ring.

Many of the trioxadispiroketal-containing natural products isolated from nature possess interesting and potent biological activities. The use of these compounds in medicine is well founded, however limited natural supplies often require synthetic methods for their production

and sale. Routes toward the trioxadispiroketal portions of these natural products is reviewed in detail later in this introduction, however to fully understand the research the chemistry and conformational aspects of spiroketals must be examined.

Conformational Aspects of Trioxadispiroketal

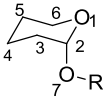
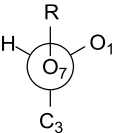
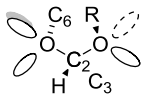
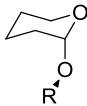
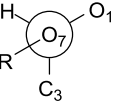
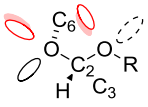
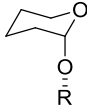
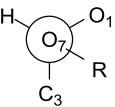
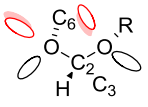
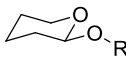
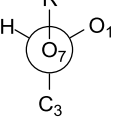
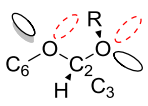
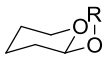
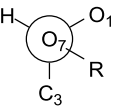
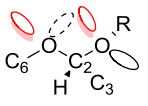
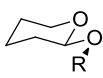
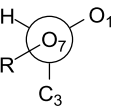
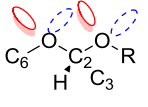
In order to develop new methodologies towards trioxadispiroketal synthesis, it is imperative to understand their chemical nature. Trioxadispiroketal characteristics resemble that of spiroketals, however, making conformational predictions is difficult due to their added structural complexity. The conformations of spiroketals are generally governed by the following factors: anomeric effects, steric influences, and intramolecular hydrogen bonding or chelation. If these factors combine, conformational predictions can be made with some confidence. When one of these preferences is compromised, conformational predictions become complicated.

The anomeric effect, first discovered by Lemieux,²¹ is a phenomenon whereby electronegative groups at C₂ prefer the axial orientation on tetrahydropyranyl rings. This preference opposes what is seen in cyclohexane systems where sterically driven equatorial conformations are favored to avoid 1,3-diaxial interactions and gauche interactions within the ring. Exactly what influences give rise to the anomeric effect and to what degree each contributes is under debate. The observed thermodynamic stability derived from the anomeric effect is currently reasoned in several different ways: minimization of electrostatic repulsions between electron pairs of the ring oxygen and the exocyclic C-O bond,²² reduction of the molecule's overall dipole moment, and increases in hyperconjugative effects.²³

The repulsion of *syn*-axial electron pairs is otherwise known as the “rabbit-ear effect.”²⁴ This disfavored effect involves unshared electrons on nonadjacent atoms residing parallel to one another. These high energy conformations are disfavored due to repulsion experienced by the

electric dipoles on the lone pairs. When a lone pair-containing substituent is positioned axially, rabbit ear effects are minimized, as opposed to equatorial positions. Table 4.1 illustrates this point.²⁵

Table 4.1: Rabbit-Ear Effects Associated with Tetrahydropyranyl Ring Conformations

Entry	Ring Conformation	Newman Projection	O-C-O Moiety Conformation	Number of Rabbit Ear Effects
1				0
2				1
3				1 (unstable)
4				1
5				1
6				2

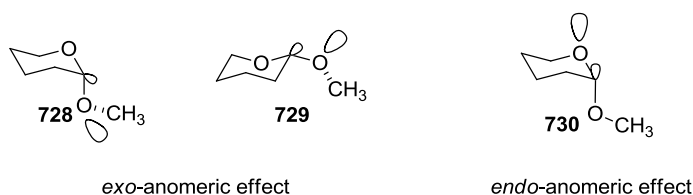
When the oxygen substituent is axial, rabbit-ear effects are minimized, and a maximum of one set of electron pair repulsions results within the system (entries 1-3). Syn axial electron repulsion is further minimized by a within-the-plane arrangement of the pendant ether group to the ring (entry 1). The conformation that brings the pendant ether group towards the inside of the chair is highly unstable due to steric interactions with the ring (entry 3). When the substituent is held equatorially, either one (entries 4 and 5) or two rabbit-ear effects (entry 6) are

experienced. In each of these conformations there is at least one electronic interaction between the tetrahydropyranyl ring oxygen and the oxygen held equatorially on the ring.

The minimization of rabbit-ear effects on tetrahydropyranyl ring systems therefore favors conformations where lone-pair bearing substituents adjacent to the ring oxygen are positioned axially. Furthermore when an electron-withdrawing substituent is held axially, the overall dipole moment of the molecule is reduced, which favors its formation in nonpolar solvents. Although these two factors contribute to the anomeric effect, hyperconjugative effects are thought to have greater influence over the ring conformation.

Hyperconjugative effects, described by Altona, arise from a $n\text{-}\sigma^*$ donation of electrons,²³ and includes both an *exo* and *endo* component. The *exo* anomeric effect relates to the exocyclic substituent's ability to donate electrons from its lone pair into the σ^* orbital of the ring oxygen. Maximum stabilization occurs when both orbitals are in a synperiplanar arrangement to one another (Figure 4.5). The *exo* anomeric effect transpires when the substituent is located at either axial (**728**) or equatorial (**729**) positions.²⁶

Figure 4.5

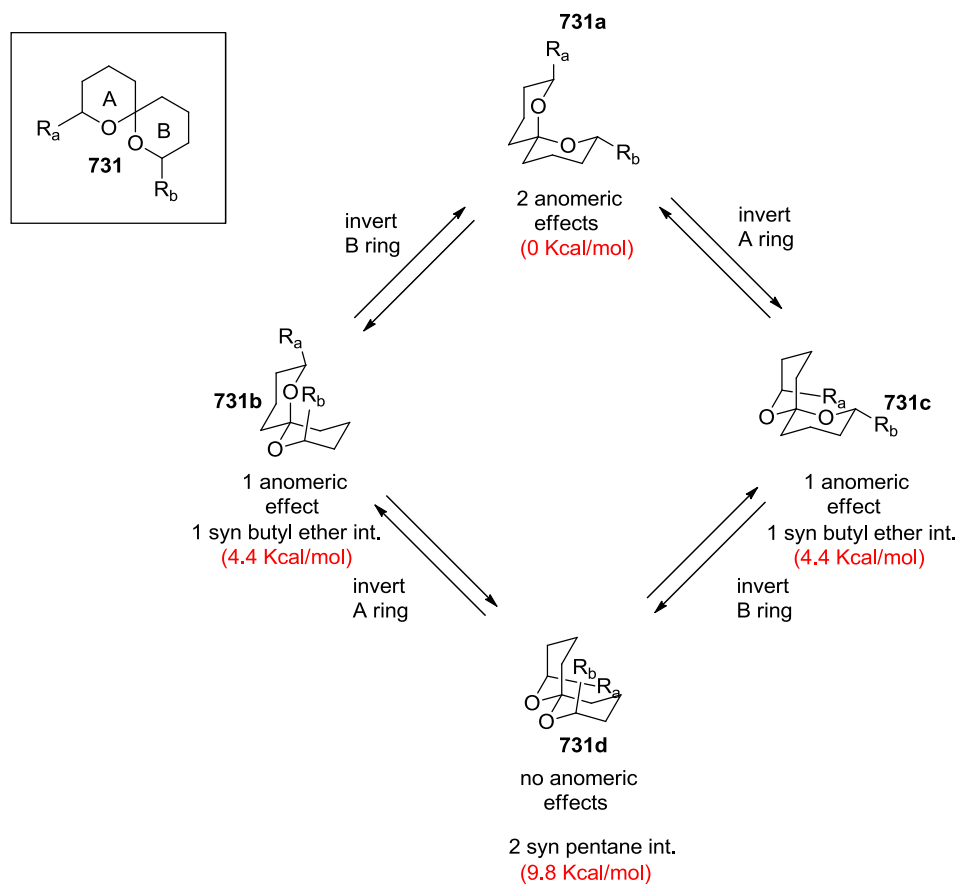


The *endo* anomeric effect relates to the donation of the endocyclic oxygen's lone pair into the σ^* orbital of the exocyclic C-O bond (**730**). This effect can only occur when the substituent is axial. The *exo* and *endo* anomeric effects exist in competition with one another, and as the electronegativity of the *exo* substituent increases, the *endo* anomeric effect is of greatest influence. Since the *endo* anomeric effect is greatest in rings with electronegative anomeric

substituents, such as oxygen in the case of spiroketals, this phenomenon helps to govern the conformation of spiroketal rings, with axial heteroatom substitution preferred.²⁷ The anomeric effect, influenced by rabbit-ear effects, molecular dipoles, and hyperconjugative effects, has a profound influence on the stability of spiroketals and highly influences their favored conformations.

The most stable spiroketal conformation is one that maximizes anomeric effects while also minimizing non-bonding interactions. For the unsymmetrically substituted spiroketal system **731** there are four possible chair conformations where conformation **731a** is favored (Scheme 4.3). Both ring oxygens are axially positioned with respect to the other ring in this conformation. This orientation gives rise to two anomeric effects. Steric interactions are

Scheme 4.3



concurrently minimized with both A and B substituents equatorial.²⁸ The relative energies of each conformation are listed for each conformation along with the associated anomeric effects and non-bonding interactions.

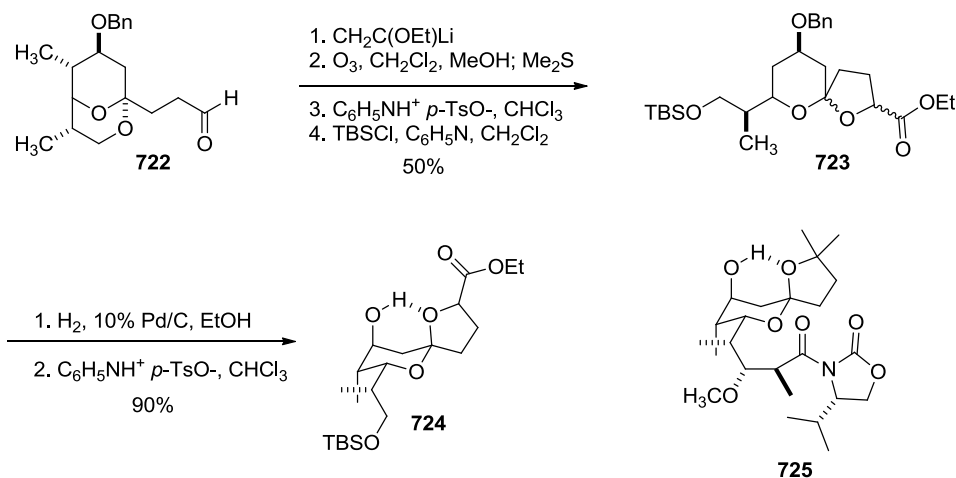
By inverting ring A, the oxygen within the B ring is now equatorial to the A ring. Thus only one anomeric effect exists in conformation **721c**, found between the endocyclic B oxygen and the oxygen held axially to ring B. This conformation also exhibits non-bonding interactions including one gauche pentane, two gauche butane, and more notably one syn-butyl ether interaction.

Inversion of the B ring in conformer **721a** gives rise to conformation **721b**, which is energetically equivalent to conformer **721c**. Again only one anomeric effect occurs due to one of the oxygens being placed equatorially. Both the reduced anomeric stabilization coupled with the increase in non-bonding interactions makes these conformations considerably less stable (ca. 4.4 Kcal/mol) than conformer **721a**. Inversion of both the A and B rings gives rise to conformer **721d**, which has no anomeric stabilization effects and two highly unfavorable syn-pentane interactions. This conformer is by far the least stable (ca. 9.8 Kcal/mol) of the four. Therefore a spiroketal of this type will favor conformation **721a** due to its high stability. These general principals of increased anomeric stabilization and decreased steric interactions can be extrapolated to similar spiroketal systems which possess substitution at other positions.

Hydrogen-bonding and chelation also contribute to spiroketal stability in specific cases. Hydrogen-bonding is prevalent in tetrahydropyranyl systems containing axial alcohols along with axial C-O spiro bonds. However intramolecular hydrogen-bonding has only been shown to influence spiroketal conformations in aprotic solvents. Ireland demonstrated the formation of spiroketals which possess hydrogen-bonding in work reported toward the synthesis of monesin

(Scheme 4.4).²⁹ Spiroketalization of precursor **722**, produced spiroketal **723** as a mixture of four diastereomers. A single spiroisomer could be obtained upon debenzylation and subsequent

Scheme 4.4

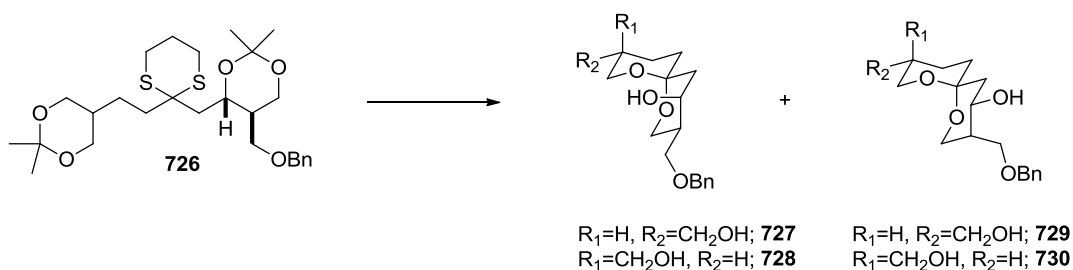


equilibration of isomers **723** using pyridinium *p*-toluenesulfonate (ppts). Although ring conformation **724** benefits from stabilizing intramolecular hydrogen-bonding between the axial alcohol and the oxygen of the furan ring, it also possesses anomeric stabilization whereas the other chair isomer would not. Nonetheless the existence of a hydrogen bond was established by a sharp O-H absorption at 3560 cm^{-1} in the IR spectrum. Similarly, Walba's synthetic work toward monesin confirmed that hydrogen bonding exists in a similar intermediate, **725**, via X-ray crystallography.³⁰ While these studies show the existence of hydrogen-bonding in spiroketal systems, they do not conclusively demonstrate how this stabilizing force directs conformational preferences.

Intramolecular hydrogen bonding is significantly affected by the solvent used in the equilibration process. These effects were demonstrated in Schreiber's work toward the synthesis of talaromycins A and B.³¹ Deprotection and cyclization of acetal **726** led to a mixture of spiroketal products, the ratio of which is dependent on the spiroketalization conditions, as

demonstrated in Table 4.2. In many cases (entries 2-6), conditions are used that give rise to a thermodynamic ratio of products. The kinetic ratio of products is shown in entries 1a-c, whereby spiroketals **729** and **730** are formed in only slight excess. The use of polar solvents, which act as

Table 4.2: Cyclization Conditions for Spiroketal Formation



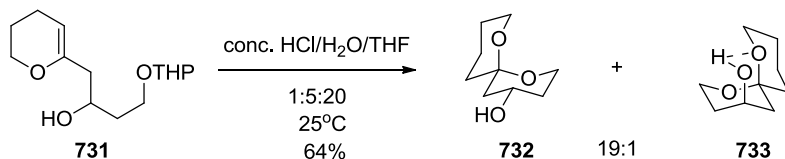
Entry	Conditions	Spiroketal Ratios			
		727	728	729	730
1	a. Amberlyst-15/MeOH b. Hg(OAc) ₂ /CH ₃ CN/H ₂ O c. 10% aq AcOH/Et ₂ O	1.1	1.0	2.4	1.8
2	CSA, CH ₂ Cl ₂	17.4	4.0	2.8	1.0
3	ZnCl ₂ , CH ₂ Cl ₂	66.0	29.0	4.0	1.0
4	2N HCl (aq) THF (1:5)	4.6	1.0	5.5	1.2
5	CSA, MeOH	4.7	1.0	6.6	1.6
6	CSA, DMSO	4.6	1.0	17.2	3.4

hydrogen bond acceptors, favored formation of spiroketals **729** and **730** (entries 4, 5 and 6). Use of non-polar, aprotic solvents produced spiroketals **727** and **728** as the major isomers (entries 2 and 3). These results can be explained as follows: In non-polar, aprotic solvents like CH₂Cl₂ (entries 2 and 3), the axial alcohol can readily form an intramolecular hydrogen-bond to the tetrahydropyranyl ring oxygen, and acts to stabilize that conformation, giving rise to **727** and **728** as the major spiroketal isomers. However, when polar solvents like DMSO are used (entries 4-6) that are capable of making intermolecular hydrogen bonds, the alcohol instead readily hydrogen-

bonds with the solvent. The alcohol substituent resides equatorially in these cases to avoid 1,3-diaxial interactions.

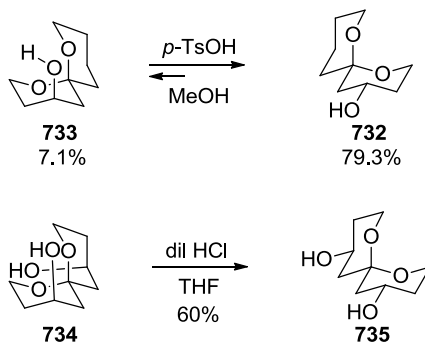
Non-intramolecularly hydrogen-bonded spiroketal isomers were favored in the synthesis of 1,7-dioxaspiro[5,5]undecanes (Scheme 4.5) using solvents containing protic species.³² Acid

Scheme 4.5



catalyzed cyclization of dihydropyran **731** in polar protic solvent produced isomers **732** and **733**, 19:1 respectively, favoring the equatorial alcohol spiroketal isomer. These results favor those published by Mori,³³ which demonstrate the greater stability of spiroketal **732**. When spiroketal **733** was subjected to protic conditions (Scheme 4.6) of acid in methanol, a mixture of spiroketals **732** and **733** resulted as a 88:7 mixture. Although the product ratios differ slightly, in both cases spiroketal **732** is preferred.

Scheme 4.6

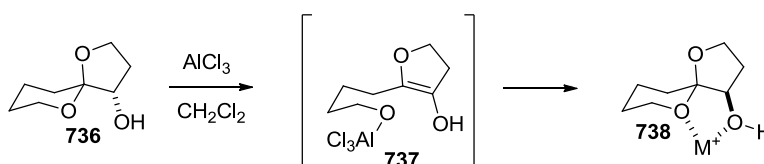


Bis-diaxial diol **734** was also isomerized to the all-equatorial isomer **735** using dilute acidic conditions. From these examples we can infer that generally equatorial alcohols are

avored on a steric basis, however, in some cases intramolecular hydrogen bonding can control spiroketal conformation, especially in non-polar, aprotic solvents.

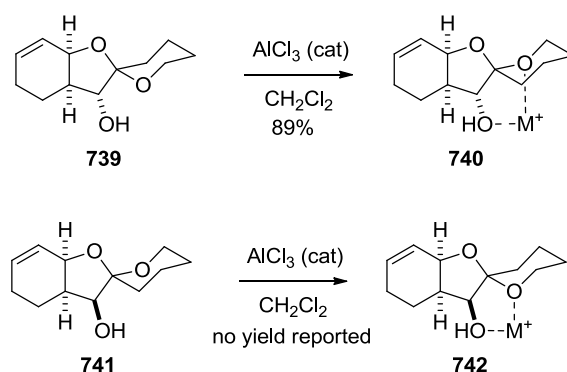
Chelation effects also effect spiroketal conformation. Descotes has shown spiroketal **53** to isomerize to spiroketal **54** under Lewis acidic conditions, by epimerizing the carbon α to the spirocenter (Scheme 4.7).³⁴ Bidentate chelation of a Lewis acid to the tetrahydropyranyl oxygen

Scheme 4.7



and alcohol substituent favors formation of isomer **738** over **736**, where bidentate chelation is not possible. Under similar conditions, tricyclic spiroketal **739** readily isomerizes to the more stable, bidentate-chelated spiroketal **740** (>20:1, **740**:**739**) (Scheme 4.8).³⁵ Likewise, spiroketal **741** isomerizes to spiroketal **742** (5:1, **742**:**741**).

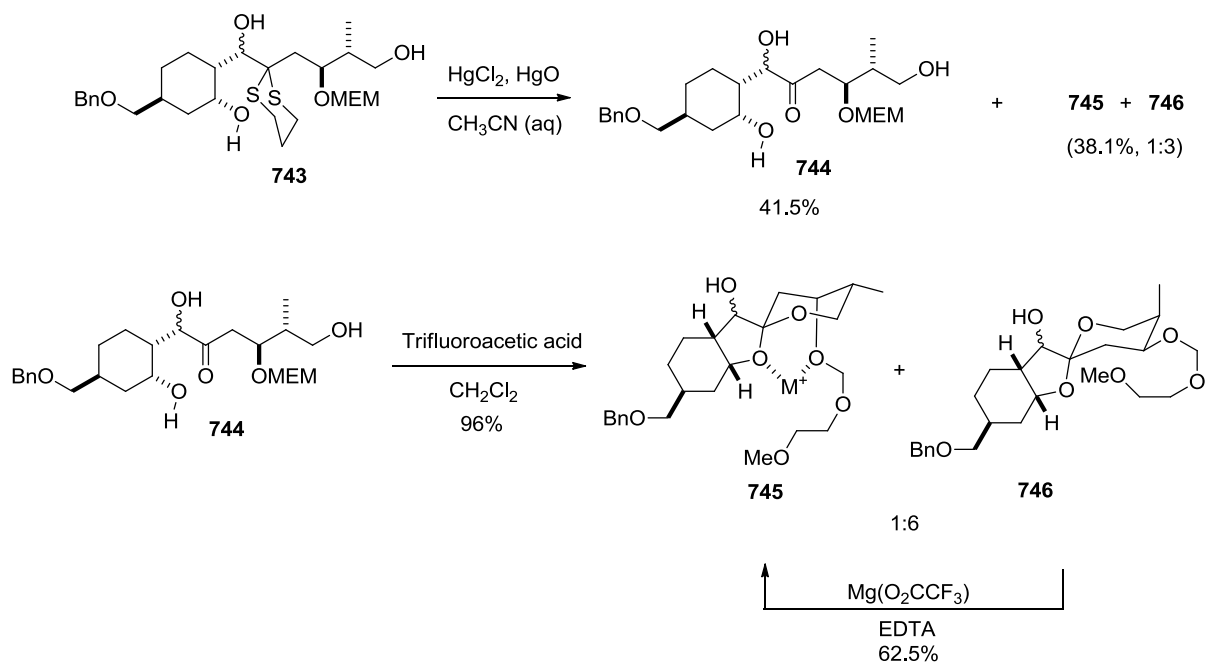
Scheme 4.8



Chelation controlled spiroketalization has been used to drive kinetic product ratio toward the thermodynamic product. Dithiane **743** was deprotected and partially cyclized to produce both ketone **744** and spiroketals **745** and **746** in a 1:3 ratio respectively (Scheme 4.9).³⁶ Secondary subjection of ketone **744** to acidic conditions successfully produced spiroketals **745** and **746** as a

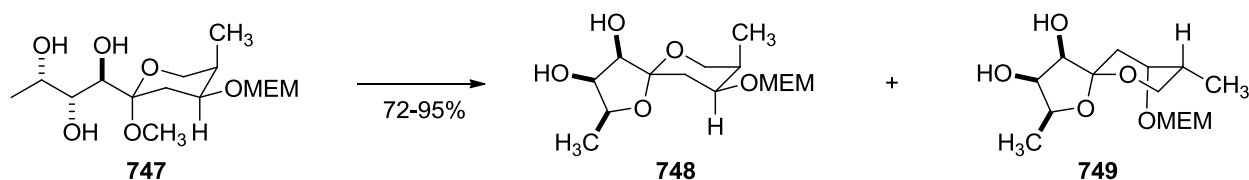
1:6 ratio of isomers. The favored spiroketal isomer produced in these cases (**745**) was not that which was desired (**746**). Fortunately, subjection of spiroketal isomer **745** to magnesium trifluoroacetate resulted in isomerization to spiroketal **746**, due to the favorable, stabilizing bidentate chelation that occurs between the Lewis acid, the tetrahydrofuranyl oxygen, and the pendant tetrahydropyranyl oxygen under these conditions.

Scheme 4.9



Similarly, Williams also demonstrated that the ratio of isomers formed from the spiroketalization of 1- γ -hydroxy-1-methoxy-tetrahydropyrans is highly dependent upon reaction conditions (Scheme 4.10).³⁷ For example, subjection of tetrahydropyran **747** to both kinetic and thermodynamic conditions resulted in a 3.3:1 ratio of spiroketals, favoring isomer **748**. Alternatively, the reaction of the same substrate with Lewis acidic conditions preferentially afforded the opposite isomer **749** in a 5:95 ratio. Not only is the opposite isomer produced, but in much greater selectivity. This is due to the favorable bis-chelation that occurs between the magnesium trifluoroacetate, the tetrahydrofuranyl oxygen, and the axial MEM ether.

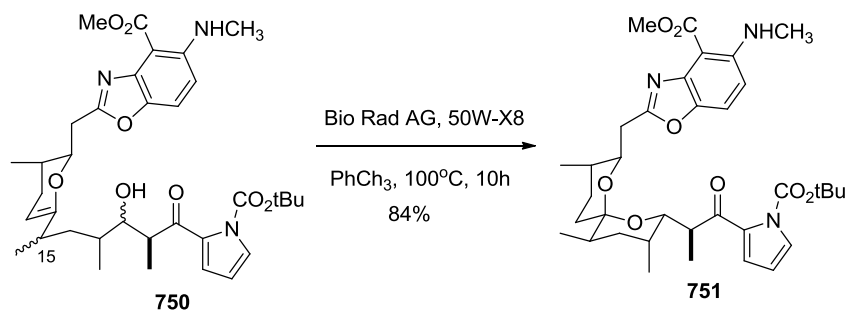
Scheme 4.10



Conditions	Product ratios (748 : 749)
PPTS, MeOH	3.3:1
TFA, CH ₂ Cl ₂	3.3:1
TFA, CH ₂ Cl ₂ , Mg(O ₂ CCF ₃) ₂	5:95

Epimerization of stereocenters α to the spirocenter has also been used in natural product synthesis. Evans took advantage of this phenomenon in his syntheses toward calcimycin (Scheme 4.11).³⁸ Upon functional group deprotection, advanced intermediate **750** was cyclized and equilibrated to afford the most stable conformers **751**. Since the α carbon of spiroketal intermediate **750** is epimerizable under acidic conditions, the stereochemistry of the methyl substituent at C₁₅ need not be set prior to spiroketalization. The methyl group epimerizes upon ring-opening of the dihydropyran to the corresponding ketone. Thus the thermodynamic product results from a process of cyclization, ring-opening, and subsequent cyclization. Here the orientation of groups about the spiro framework is controlled rather than the actual conformation

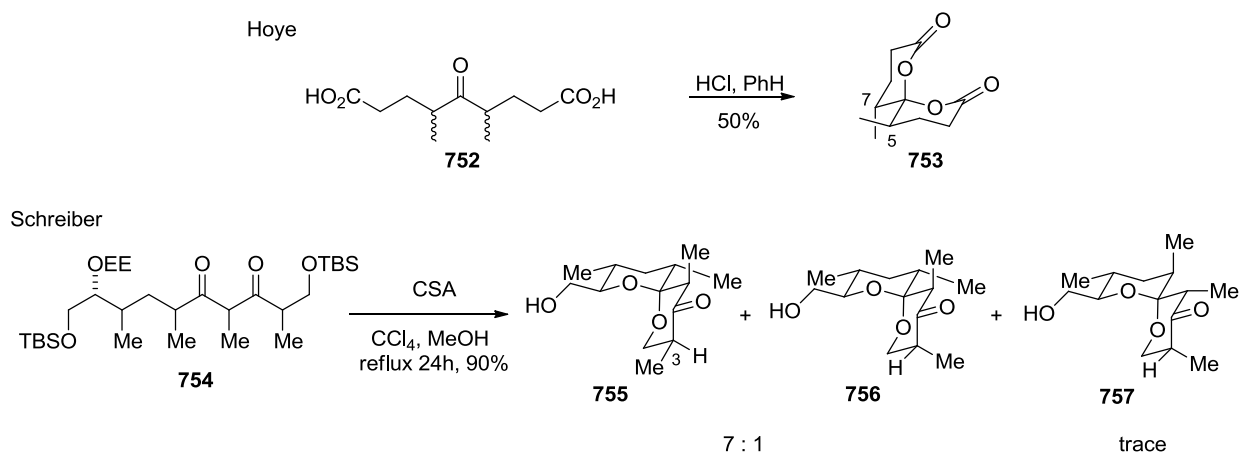
Scheme 4.11



of the spiroketal itself. By recognizing the epimerizability of these centers, both researchers were able to simplify their synthetic approach to calcimycin. In setting fewer stereocenters prior to cyclization, the efficiency of this sequence was increased. Therefore Nakahara adopted a very similar approach to calcimycin that capitalized from this simplification.³⁹

Thermodynamic equilibration to form the most stable spiroketal conformer has been similarly used in the synthesis of invictrolide. Both Hoyer⁴⁰ and Schreiber⁴¹ cyclized intermediates **752** and **754** respectively to form advanced synthetic intermediates of this natural product (Scheme 4.12). In both cases a mixture of diastereomers was thermodynamically cyclized under acidic conditions to afford bis-equatorial spiroketals **753** and **755** as the major isomers. Here, none of the C₅-C₇ axial-equatorial products were formed due to the high energy syn pentane steric interaction associated with that conformation. The ratio of isomers **755** to **756** is representative of the energetic difference between these two conformations where the C₃ methyl group prefers an equatorial position. Only a trace of the axial-axial isomer **757** was detected.

Scheme 4.12



Previous work has shown that anomeric effects, non-bonding interactions, hydrogen-bonding, chelation control, and epimerization of centers adjacent to the spirocenter play an

important role in the stabilization and conformational preferences of spiroketals. While the study of trioxadispiroketal systems has not specifically been reported, the properties of simple spiroketals can be projected onto these double spiroketal systems. The factors that control thermodynamic spiroketalization are important to consider when designing syntheses of spiroketal-containing natural products. Many investigators use these stabilizing traits to their advantage when carrying out natural product synthesis. Application of these principles to trioxadispiroketal synthesis is discussed below.

Trioxadispiroketal Syntheses

The synthesis of trioxadispiroketal is more challenging than the manufacture of simple spiroketals due to increasing steric interactions and the greater difficulty in predicting the thermodynamic preferences of a complex three-ring system. Exactly which stabilizing effects will govern the manufacture of one conformer or diastereomer over another is based on the substituents in the ring system. Therefore the synthesis of trioxadispiroketal must be carefully evaluated on a case by case basis.

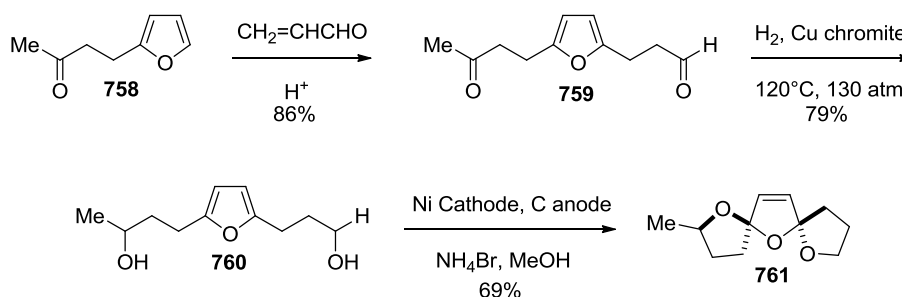
When working toward the manufacture of natural product-based bis-spiroketal, the thermodynamic isomer is typically that desired. For this reason, acid catalyzed cyclization of a ketone or similar moieties is a viable route. Other methods used include oxidative cyclization and Norrish type II cleavage. These methods have been used for the synthesis of (5,5,5), (5,6,5), (6,5,6), (6,6,6), and (5,6,6)-trioxadispiroketal systems.

Synthesis of 1,6,8-trioxadispiro[4.1.4.2]tridecanes

The synthesis of a trioxadispiroketal was first reported in 1963 by Ponomarev and Markushina (Scheme 4.13).⁴² Their approach to the 1,6,8-trioxadispiro[4.1.4.2]tridecane ring system involved electrolytic alkoxylation of furan **760** using a nickel cathode and carbon anode.

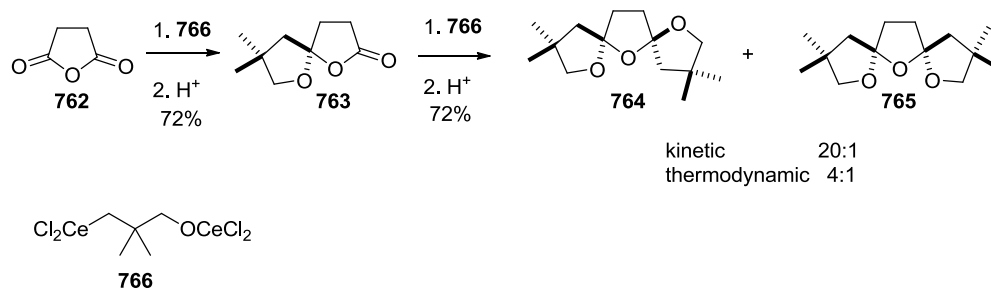
Furan **73** was constructed by acid promoted acrolein addition to furan **758**, followed by carbonyl reduction. The (5,5,5)-*trans*-bis-spiroketal diastereomer **761** was selectively formed, due to the low overall molecular dipole moment experience by this compound compared to all other possible isomers. This example proves interesting as the spiroketal system was directly formed from an aromatically stabilized furan precursor, and this required relatively strong conditions. These conditions, however, may not be accessible for every laboratory.

Scheme 4.13



Cohen designed the synthesis of 5,5,5-bis-spiroketal **764** and **765** through the consecutive addition/cyclization of an organocerium reagent to succinic anhydride **762** (Scheme 4.14).⁴³ Addition of Cerium 3-ceriopropoxide **766** to succinic anhydride, followed by an acidic workup provided spiro lactone **763** in 72% yield. Subsequent addition of a second equivalent of

Scheme 4.14



the cerium reagent **766** yielded spiroketals **764** and **765** as a 20:1 mixture of diastereomers. Under thermodynamic conditions a 6:1 ratio of diastereomers was realized. The requisite

organocerium reagent was readily prepared by addition of LDBB to 3,3-dimethyloxetane followed by treatment with CeCl₃.⁴⁴ The use of organocerium reagents is superior to other organometallics in this application. For example, addition of similar organolithium reagents to succinic anhydride gave only a 13% yield of lactone product **763**. Overall this sequence provides a rapid, highly convergent preparation of the 5,5,5-bis-spiroketal core, though yields are variable in other systems.

1,6,8-Trioxadispiro[4.1.4.3]tetradecane Synthesis

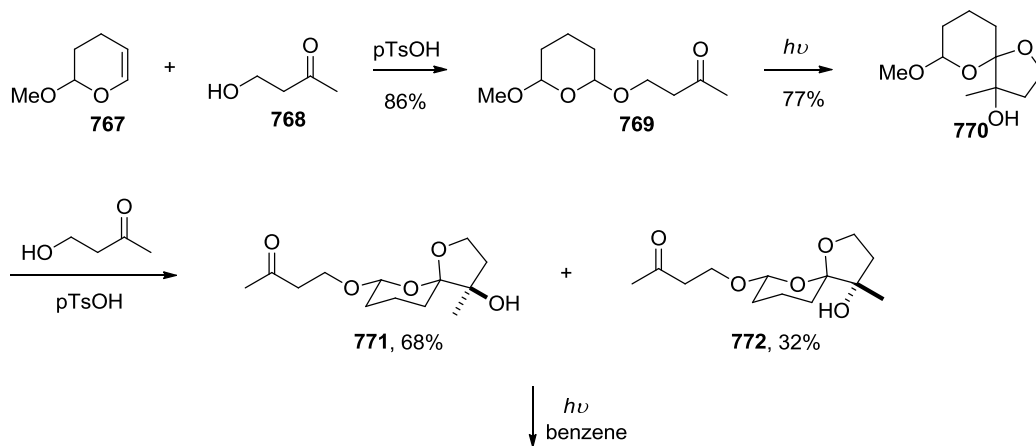
(5,6,5)-Trioxadispiroketal systems were studied by Descotes, who applied Norrish type II reactions toward their synthesis (Scheme 4.15).⁴⁵ Dihydropyran **767** was combined with alcohol **768** under acid catalysis to form ketal **769**. Subsequent photolysis of tetrahydropyran **769** and cyclization of the resulting diradical yielded spiroketal **770** as a mixture of isomers that were carried forward together. Transketalization of spiroketal **770** with alcohol **768** provided spiroketals **771** and **772**, which were separated and individually irradiated to form the trioxadispiroketal products (**773-778**). Irradiation of spiroketal **771** yielded products **773-776**. Likewise treatment of spiroketal **772** produced products **776-778**.

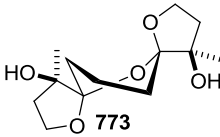
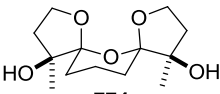
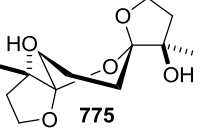
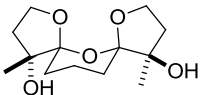
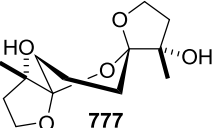
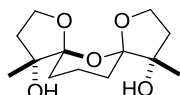
Norrish type II conditions provided kinetic cyclization products, and resulted in poor diastereomer product mixtures. Note that bis-spiroketals **773**, **775**, and **777** adopt a twist boat-like conformation for two reasons; this conformation maximizes stabilizing anomeric effects while decreasing unfavorable 1,3-diaxial interactions. This work demonstrated the success in using Norrish type II cyclization strategy toward bis-spiroketal synthesis although poor product mixtures result.

Synthesis of 1,7,9-trioxadispiro[5.1.5.3]hexadecanes

(6,6,6)-Trioxadispiroketal systems have been synthesized using both oxidative cyclization with hypoiodite (Scheme 4.16) and acid catalyzed cyclization. Alcohol **781** was prepared by nucleophilic addition of allyltributyltin reagent **780** to the oxonium ion generated

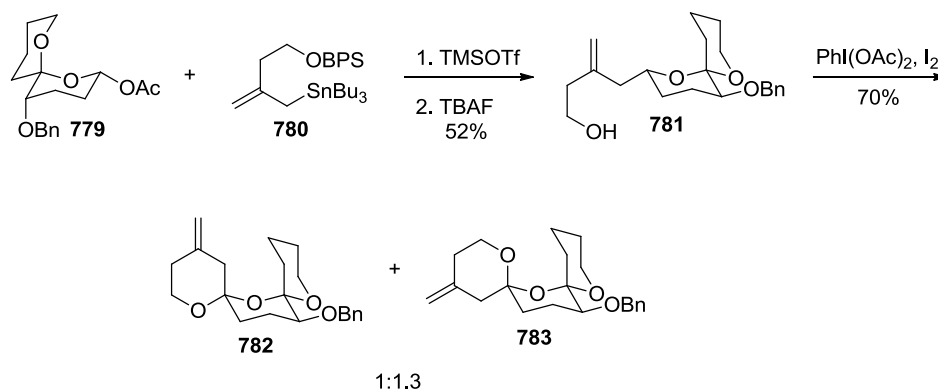
Scheme 4.15



Substrate	Products	
771	 773 31%	 774 5%
771	 775 18%	 776 11%
772	775 , 28%	776 , 16%
772	 777 15%	 778 13%

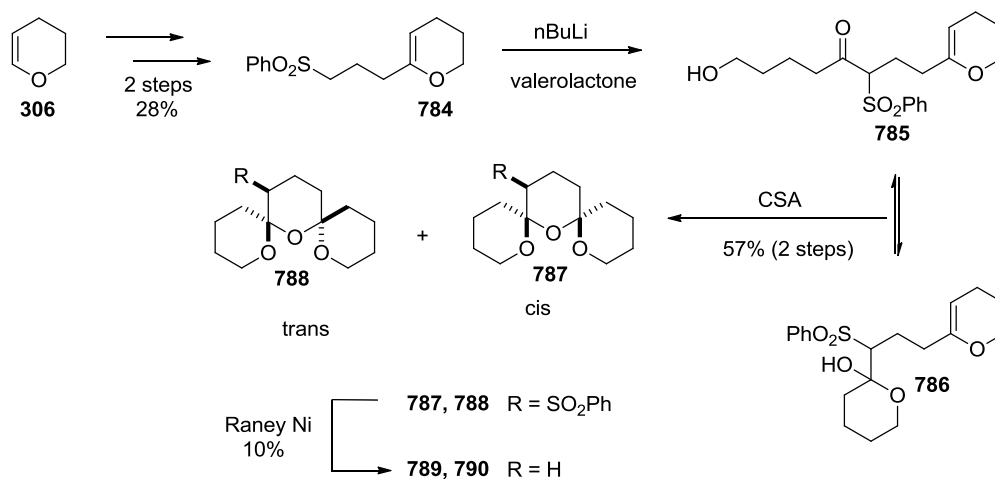
from the advanced spiroketal intermediate **779**.⁴⁶ Subsequent deprotection provided alcohol **781** in moderated yield. This alcohol was then oxidatively cyclized by irradiation in an iodobenzene diacetate solution containing iodine to kinetically form trioxadispiroketal **782** and **783** as a 1:1.3 kinetic ratio of products. The poor product ratio, minimally favors formation of anomERICALLY stabilized bis-spiroketal **783**.

Scheme 4.16



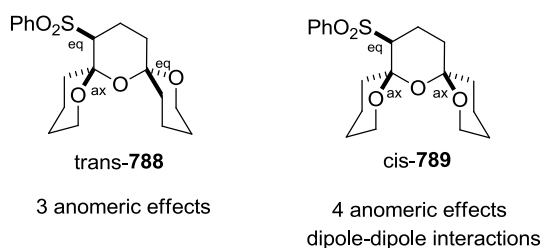
Brimble employed acid catalyzed cyclization to synthesize phenylsulfonyl bis-spiroketal **787** and **788** from 3,4-dihydropyran **306** (Scheme 4.17).⁴⁷ Sulfone **784** was synthesized from

Scheme 4.17



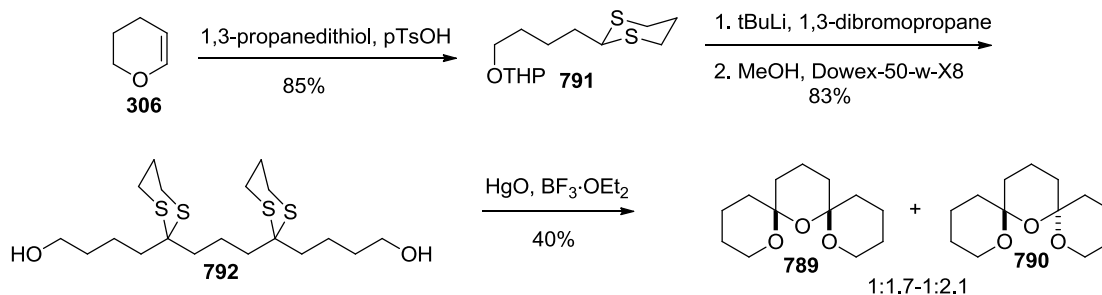
dihydropyran **306** over 2 steps in 28% yield. This intermediate was subsequently deprotonated and added to δ -valerolactone to provide keto alcohol **785** that lies in equilibrium with cyclic hemiacetal **786**. Direct cyclization of the mixture under acidic conditions provided bis-spiroketal **787** and **788** as a 1:1 mixture of *cis* and *trans* diastereomers in 57% yield over two steps. These isomers were then individually reduced to provide bis-spiroketal **788** and **790**. The poor diastereomeric ratio is the result of the two products having similar stabilities. Although in theory the *cis* isomer is stabilized by four anomeric effects, the *trans* isomer benefits from a more favorable overall dipole moment (Figure 4.6).

Figure 4.6



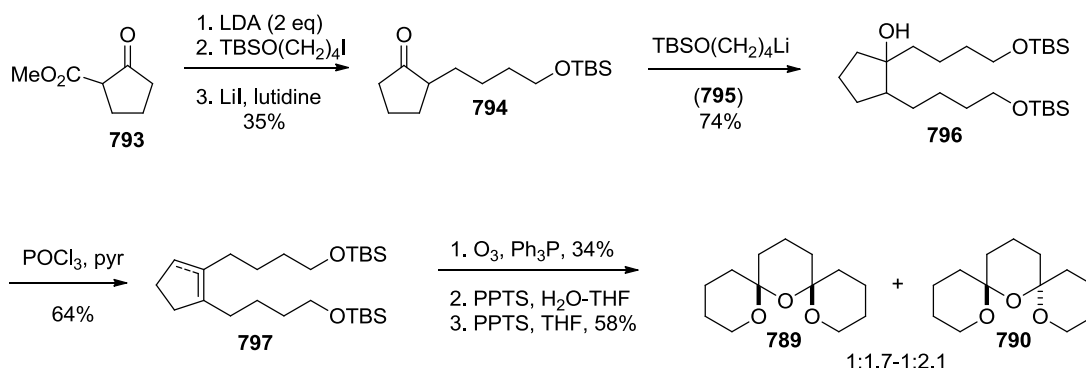
McGarvey synthesized unsubstituted (6,6,6)-bis-spiroketal systems by acid catalyzed cyclization in an attempt to both improve yield as compared to the Brimble synthesis while also studying the relative stabilities of the *cis* and *trans* isomers.⁴⁸ McGarvey devised three approaches to this system. The first synthetic approach involved addition of propanedithiol to 3,4-dihydropyran **306** to create dithiane **791** (Scheme 4.18). Addition of two equivalents of the deprotonated dithiane **791** to 1,3-dibromopropane afforded diol **792** after alcohol deprotection. Removal of dithiane protecting groups and Lewis acid catalyzed cyclization yielded *cis* and *trans*-bis-spiroketal **789** and **790** (1:1.7-1:2.1) in 32% and 28% yields respectively. The yields for this synthetic pathway are far greater than Brimbles (1.6%). The *trans* diastereomer was produced in excess of the *cis* due to the lesser overall dipole moment in that molecule, although *cis* diastereomer **789** benefits more from anomeric effects.

Scheme 4.18



The second approach to this system by the same group involved preparation from substrates where asymmetry could be more easily introduced into the bis-spiroketal (Scheme 4.19). Alkylation of keto ester **793** followed by Krapcho decarboxylation gave ketone **794**.⁴⁹ Subsequent addition of organolithium **795** to ketone **794** yielded alcohol **796**. Elimination was followed by oxidative cleavage and acid catalyzed deprotection-cyclization to afford spiroketals

Scheme 4.19



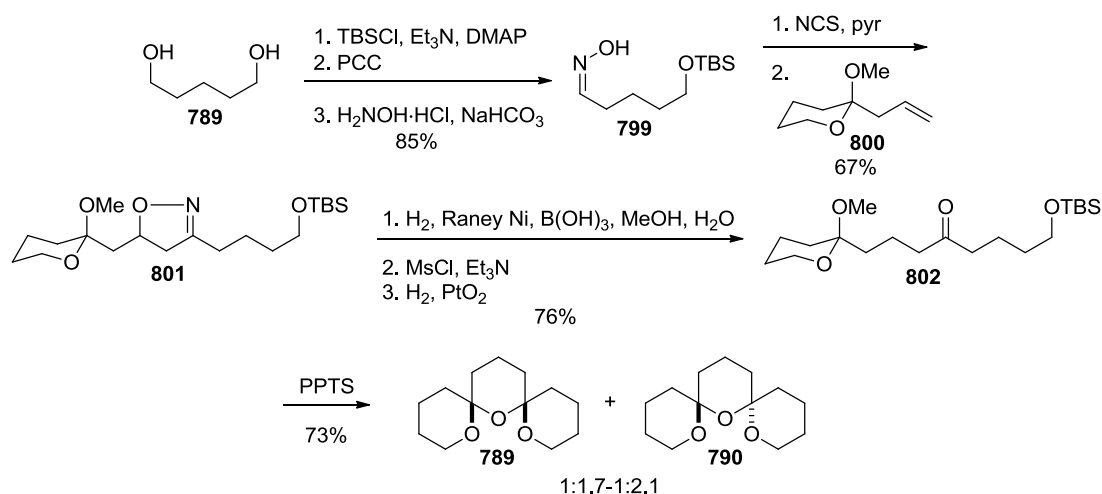
789 and **790**. The overall yield of this process was relatively low (3.3%), and therefore led to an alternate approach of these bis-spiroketal products where asymmetry could be easily introduced (Scheme 4.20).

McGarvey's third approach provided the desired spiroketals in good overall yield (32%). The carbon skeleton of the trioxadispiroketal was constructed through 1,3-dipolar addition of a nitrile. Monoprotection, and oxidation of 1,5-pentanediol **798** was followed by conversion to .

Oxime **799**. 1,3-dipolar addition of nitrile oxide **799** to olefin **800** yielded isoxazoline **801**. Reductive cleavage of the N-O bond was followed by elimination of the mesylated β -hydroxyketone. Subsequent hydrogenation of the olefin afforded ketone **802**. Acid cyclization with PPTS yielded spiroketals **789** and **790** (1:2.1) in an overall yield of 32%.

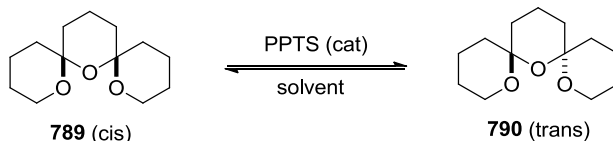
The work of Brimble and McGarvey demonstrates the success of acid catalyzed cyclization toward trioxadispiroketal synthesis, although these (6,6,6)-systems provide little

Scheme 4.20



diastereoselective preference. McGarvey studied these trioxadispiroketal further to examine their conformations and determine what relative energy difference exists between the two isomers. Subjection of each bis-spiroketal to thermodynamic conditions resulted in favored production of the trans isomer, where the ratio of isomers was slightly based on solvent effects (Table 4.3). The use of non-polar solvents resulted in spiroketal ratios clearly favoring the trans isomer. Alternatively, use of polar solvents like DMSO provided lower ratios presumably by stabilizing the molecular dipole experienced by the *cis*-isomer.

Table 4.3: Isomerization of 1,7,9-Trioxadispiro[5.1.5.3]hexadecanes in Different Solvents

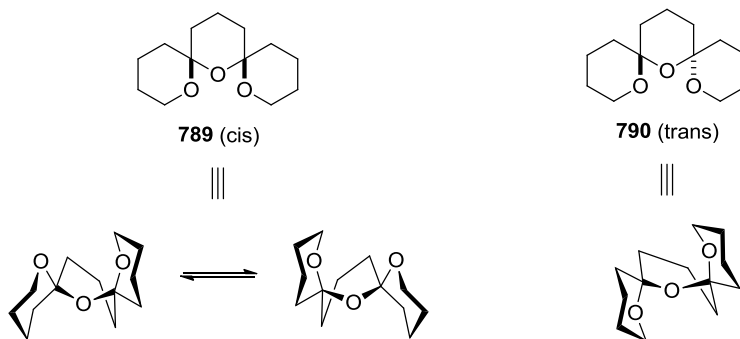


Entry	Solvent	Time (hr)	789:790
1	hexanes ¹	24	1:3.3
2	THF	69	1:2.1
3	CH ₂ Cl ₂	26	1:2.1
4	DMSO	53	1:1.8

¹CSA used as acid catalyst

Analysis of these ratios indicate that the relative energy difference between the two conformations is between 0.3-0.7 kcal/mol favoring the *trans* isomer. NMR studies of both isomers indicated that the central ring adopts a twist-boat conformation (Figure 4.7). This conformation allows for maximization of anomeric effects while concurrently alleviating both steric and dipole-dipole interactions. As a result, the *trans* isomer benefits from 4 anomeric effects, although favorable bond angles are compromised. On the other hand, the *cis* isomer

Figure 4.7



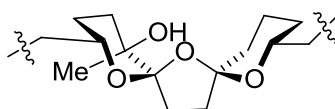
gives up one of the anomeric stabilizations to alleviate the dipole-dipole interaction it experiences. Overall the *trans* isomer is slightly preferred. These results indicate that anomeric effects cannot solely be studied for the evaluation of isomeric preference in trioxadispiroketal.

Unlike simple spiroketals, clearly dipole-dipole interactions play a critical role in the conformation preference of bis-spiroketals.

1,7,9-trioxadispiro[5.1.5.2]pentadecane Synthesis

6,5,6-Trioxadispiroketal systems have been prepared en route to the synthesis of pinnatoxin **713** (Figure 3).⁵⁰ Double anomeric effects and reduction of sterics stabilize the bis-spiroketal present in the pinnatoxins, making thermodynamic cyclization a viable ring-closing technique (Figure 4.8).

Figure 4.8



pinnatoxin trioxadispiroketal core

Murai's group was the first to synthesize the bis-spiroketal portion of the pinnatoxins as outlined in Scheme 4.21.⁵¹ The key intermediates, sulfone **804** and aldehyde **806** were each prepared in six steps from the alcohols **803** and **805** respectively. Deprotection of the sulfone **804** and addition to the aldehyde **806** then gave the hydroxyl sulfone derivative **807**. Swern oxidation, desulfonation, and oxidation of the alkyne yielded trione **808**, which upon acid catalyzed cyclization produced the desired spirocyclic pinnatoxin core **809** in good yield. The major diastereomer formed exhibits anomeric stabilization between the tetrahydrofuran ring and both tetrahydropyranyl rings. This coupled with the equatorial arrangement of substituents makes this conformer the most stable and therefore the major isomer isolated. Dipole-dipole interactions are minimized in this system as compared to the [6,6,6]-bis-spiroketal because of the placement of polar substituents, thus increasing the yield of *cis* isomer formed.

Scheme 4.21

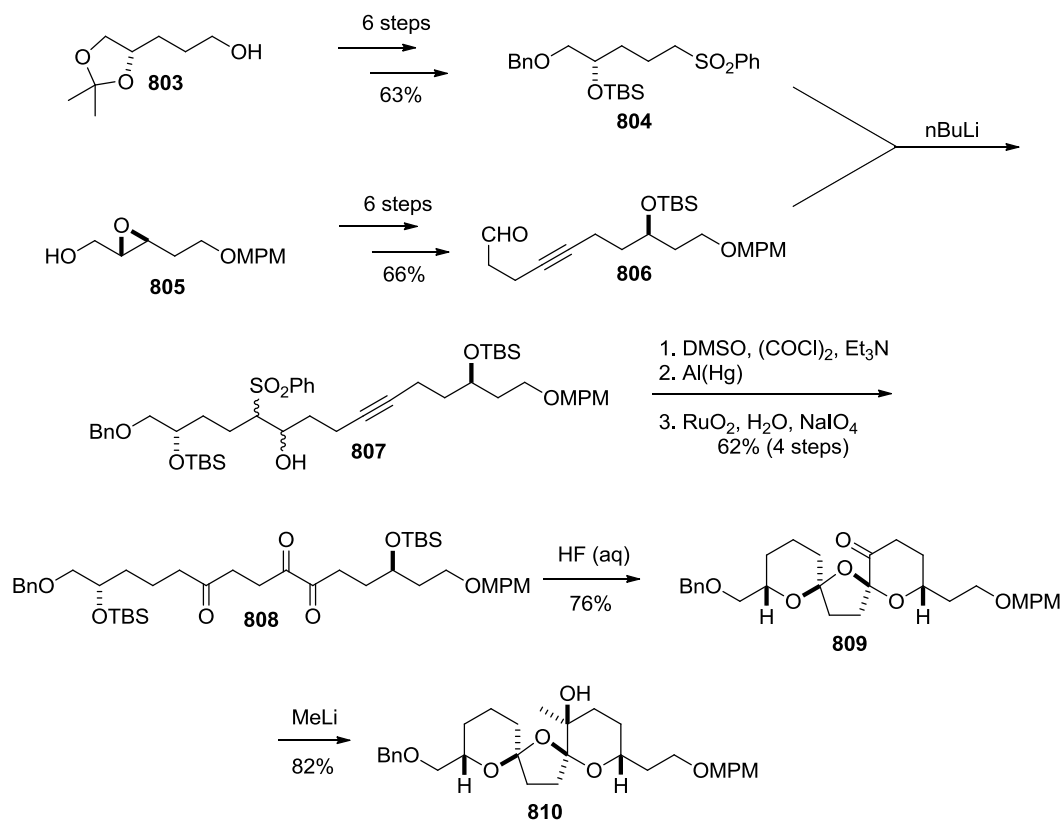
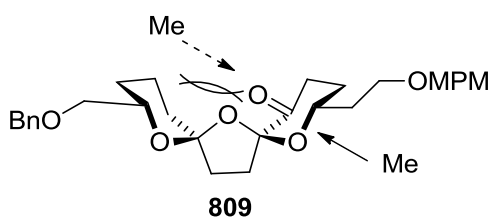


Figure 4.9

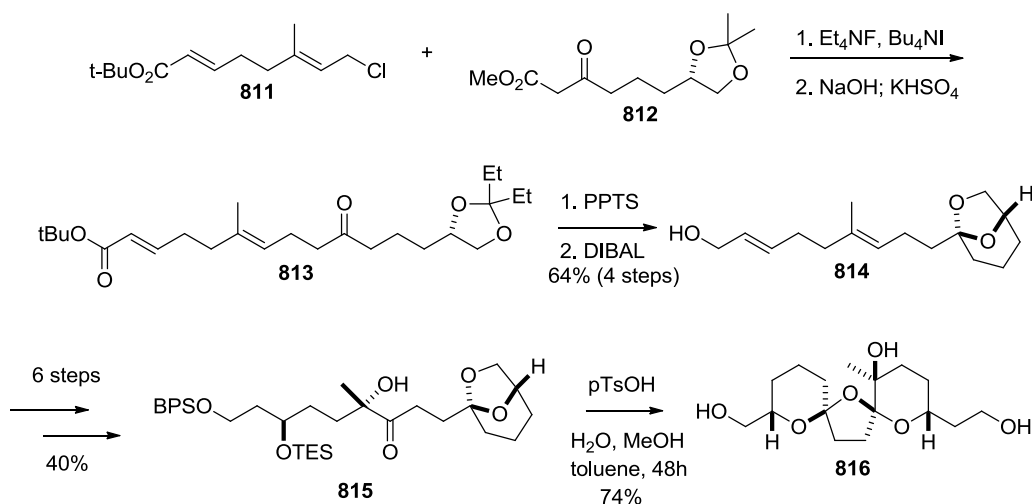


Minor diastereomers of bis-spiroketal **809** formed from this process could be re-equilibrated such that bis-spiroketal **809** was ultimately obtained in 86% yield. Addition of methyllithium to the remaining ketone moiety installed the needed methyl group stereoselectively from the less hindered, bottom face. The Murai synthesis achieved formation of the pinnatoxin trioxadispiroketal in 12 steps and 16% overall yield. The route benefits from

the convergent approach and used thermodynamic spiroketalization to produce the desired bis-spiroketal core stereoselectively.

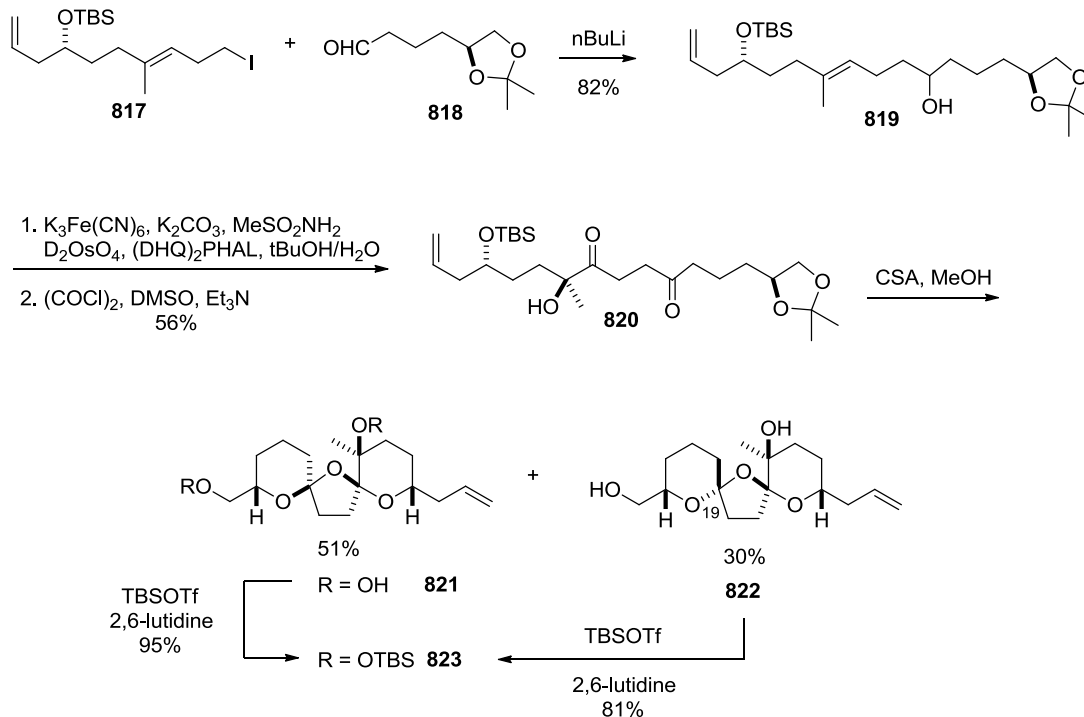
The second synthesis of the pinnatoxin trioxadispiroketal was achieved by Hirama (Scheme 4.22).⁵² Alkylation of the β -keto ester **812** with allyl chloride **811** was followed by saponification and decarboxylation to yield ester **813**. Diol deprotection and reduction of the ester led to acetal **814**, which was produced in 64% yield from ketone **813**. Acetal **814** was, in turn, converted to spiroketal precursor **815** in 6 steps and 40% yield. With acetal **815** in hand, cyclization to the desired trioxadispiroketal was possible under aqueous acidic conditions over a 48-hour period. The desired spiroketal **816** was produced as the major product (74%), with other isomers formed in 12% yield. These isomers were then re-subjected to the reaction conditions to afford the desired spiroketal. Hirama's synthesis provided the pinnatoxin bis-spiroketal core in 17% overall yield in 13 consecutive steps, similar to the results obtained by the Murai.

Scheme 4.22



A third approach to the pinnatoxin trioxadispiroketal system was reported by the Kishi group as described in their total synthesis of pinnotoxin A (Scheme 4.23).⁵³ Advanced intermediates **817** and **818** were combined through use of transmetalation to yield alcohol **819** as

Scheme 4.23



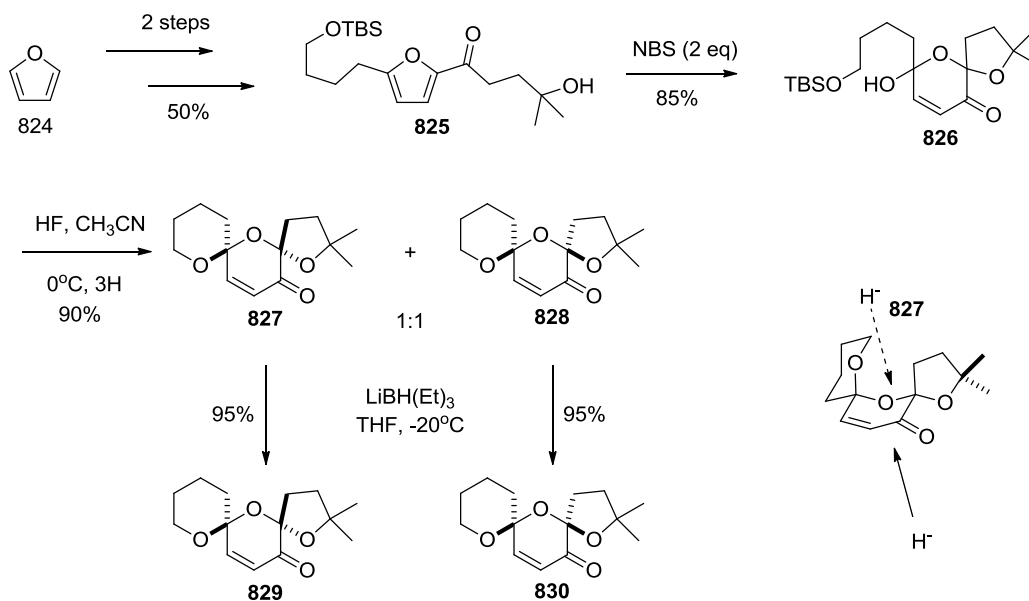
a mixture of diastereomers which were carried on together. Sharpless asymmetric dihydroxylation and subsequent Swern oxidation resulted in formation of dione **820**, which after acid induced cyclization with camphorsulfonic acid, afforded both the desired bis-spiroketal structure **821** along with the C_{19} epimer **822**. Interestingly, subjection of bis-spiroketal **822** to silylation conditions epimerized the stereocenter back to the desired configuration to provide silyl-protected bis-spiroketal **823**. Alternatively, spiroketal **821** would epimerize to bis-spiroketal **822** in the presence of magnesium bromide. Once the tertiary alcohol was converted to the silyl ether, causing it to be configurationally stable, subsequent chemical transformations were carried out without compromising the stereochemical integrity of the bis-spiroketal. Thus the core of pinnatoxin A was produced in 12% overall yield through 13 reported linear steps, which is a slightly lower yield than the Murai and Hirama syntheses. The trioxadispiroketal core

was then further manipulated and transformed into pinnatoxin A to provide the first reported total synthesis of this natural product.

Synthesis of 1,6,8-Trioxadispiro[4.1.5.3]pentadecanes

Approaches to (5,6,6)-bis-spiroketal include synthetic work towards both salinomycin **707** (Figure 4.2) and spirastrellolide A **376** (Figure 4.4) natural products. Several groups have worked towards synthesizing members of the salinomycin family of antibiotics due to their high molecular complexity and bioactivity. Model studies toward the synthesis of the salinomycins were performed by Perron,⁵⁴ Kocienski,⁵⁵ and Baker.⁵⁶ Perron created the trioxadispiroketal moiety by oxidation and cyclization of functionalized furan **136** (Scheme 4.24). Oxidation and

Scheme 4.24

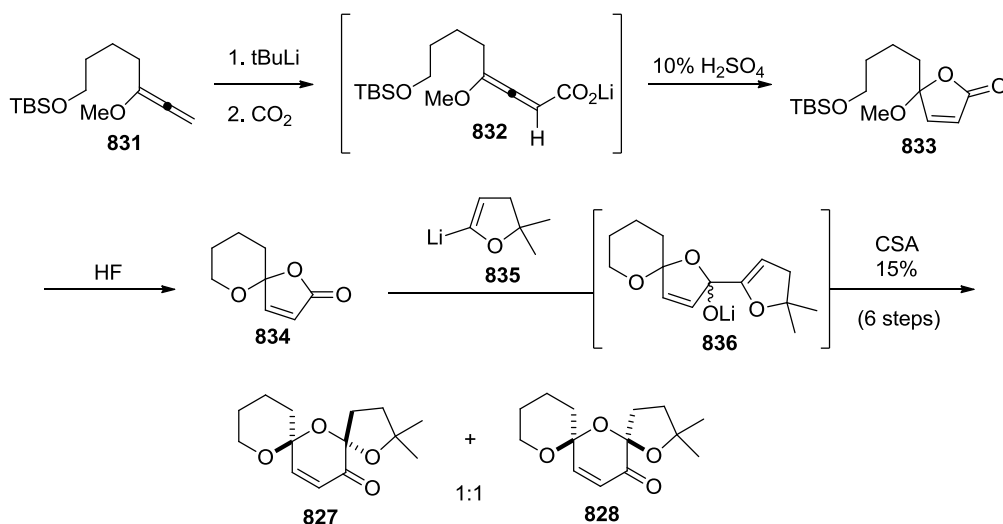


rearrangement of furan **136** using NBS yielded spiroketal **137** as an equilibrium mixture of isomers, which were carried on together. Desilylation and acid-induced kinetic spiroketalization produced bis-spiroketal **827** and **828** in 90% yield, which could then be successfully separated. Subsequent reduction of the individual isomers proceeded in good yield from the more

accessible bottom face. Overall, this synthesis provided the desired bis-spiroketal **829** and **830** in 36% overall yield from furan in 5 steps.

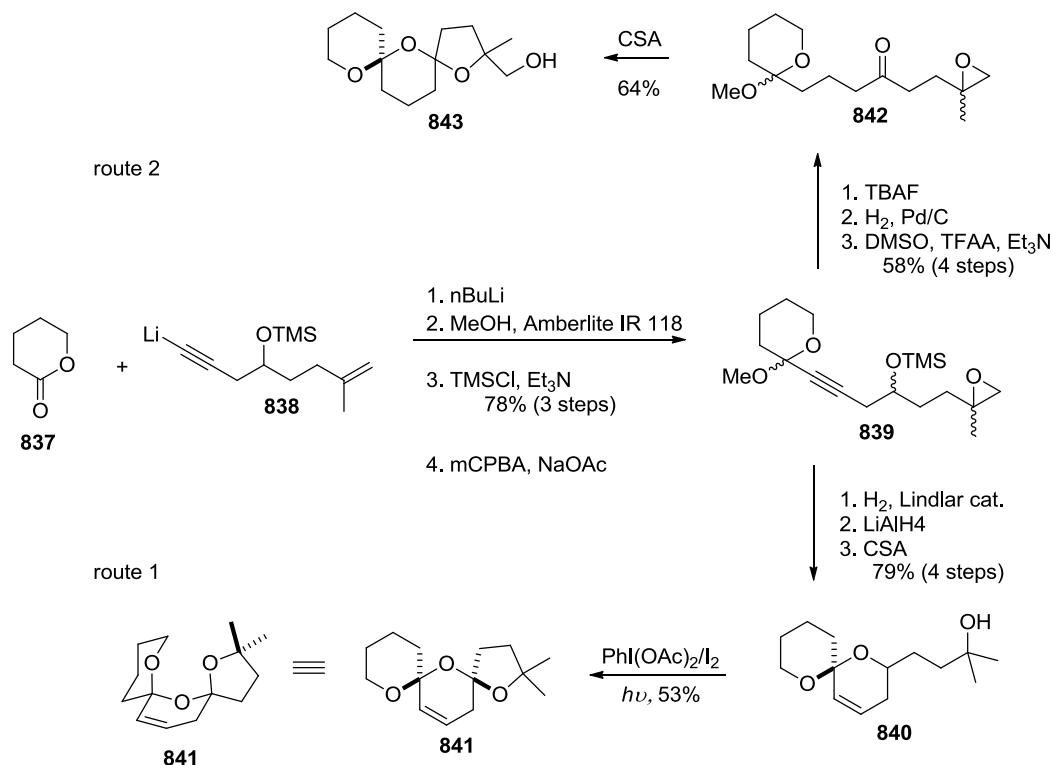
Kocienski developed an alternate approach to this spiroketal system in which methoxyallene **831** was metallated and carboxylated to yield intermediate allene **832** (Scheme 4.25).⁵⁷ Sulfuric acid catalyzed cyclization led to butenolide **833**. Subjection of the butenolide to hydrofluoric acid effected hydrolysis and secondary cyclization to give spirocyclic butenolide **834**, which was added to lithiated dihydrofuran **835** to afford the bis-dihydrofuran intermediate **836**. Cyclization with camphor sulfonic acid yielded the desired trioxadispiroketal **827** and **828** in a 1:1 mixture in an overall yield of 15% from methoxyallene **831**. Although this synthesis of the (6,6,5)-trioxadispiroketal model system is lower yielding than the route involving furan, it provides as an alternative entry to bis-spiroketal production by utilizing butenolides as intermediary structures.

Scheme 4.25



Baker approached the salinomycin ring system by two routes, which diverged from a common intermediate **839** (Scheme 4.26).⁵⁶ The first route employed oxidative cyclization to

Scheme 4.26



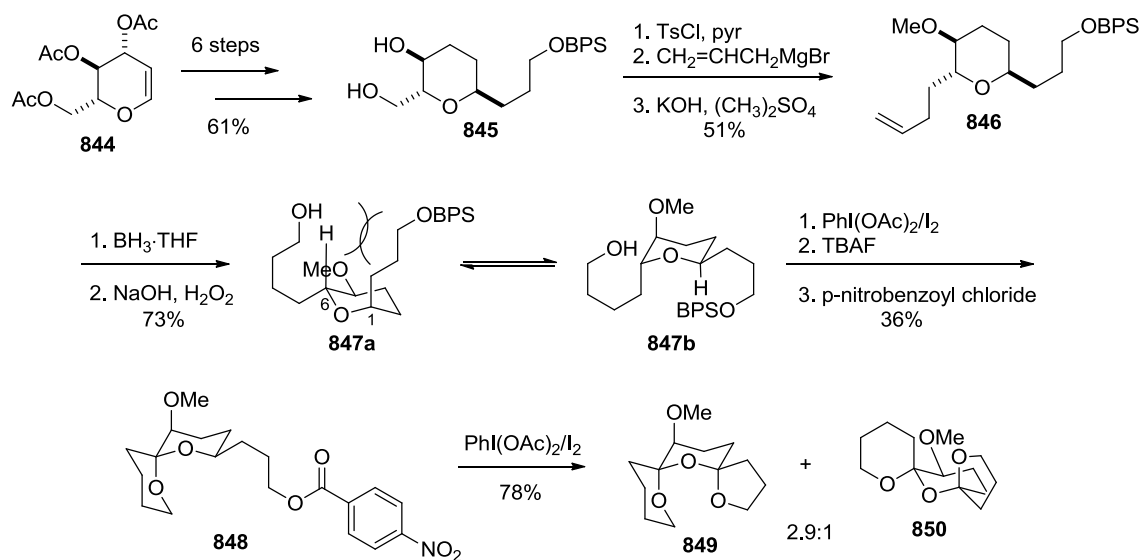
manufacture the three-ring system, while the second path utilized acidic conditions. Intermediate **839** was synthesized by addition of the lithium acetylide **838** to δ -valerolactone **837** followed by various functional group manipulations, which included non-stereoselective epoxidation. To form the olefin-containing trioxadispiroketal **841**, alkyne **839** was partially reduced to the corresponding *cis*-olefin, the epoxide was opened, and acid catalyzed ring closing by irradiation in an iodobenzene diacetate solution containing iodine formed the first spirocenter **840**. Oxidative cyclization then gave the bis-spiroketal **841**. The isomer formed was consequently that which is believed to experience the most stabilization due to anomeric effects.

The corresponding saturated trioxadispiroketal **843** was also prepared from intermediate **839**. Desilylation, full alkyne reduction, and oxidation yielded spiroketal precursor **842**, which

was transformed under acid catalyzed conditions into the single trioxadispiroketal product **843**, though the stereochemistry about the tetrahydrofuran-tetrahydropyran spirocenter was not assigned. This work demonstrated the creation of bis-spiroketals from intermediates derived from alkyne addition into lactones. This same methodology was later used by Brimble towards the total synthesis of *epi*-17-deoxy-(*O*-8)-salinomycin,⁵⁸ however late stage synthetic challenges caused this route to be abandoned.

Suarez utilized two subsequent hypervalent iodine oxidation-cyclizations toward the synthesis of (5*R*,7*S*,13*S*)-13-methoxy-1,6,8-trioxadispiro[4.1.5.3]pentadecane (Scheme 4.27).⁵⁹ Diol **845** was prepared from readily available tri-*O*-acetyl-D-glucal **844** in 61% yield over 6 steps.⁶⁰ Selective tosylation of the primary alcohol followed by displacement with allyl magnesium bromide and methylation of the remaining secondary alcohol led to alkene **846**. Hydroboration of the newly formed olefin resulted in tetrahydropyran **847a**, which is in equilibrium with conformer **847b**. Efforts to cyclize the diol version of this tetrahydropyran to

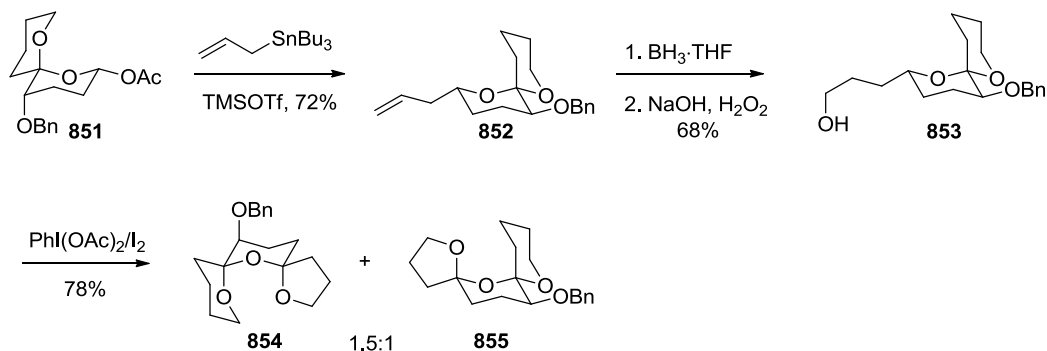
Scheme 4.27



form the bis-spiroketal were unsuccessful. It is proposed that the 5,6-spiroketal forms first, and the steric bulk of this spirocenter hinders hydrogen abstraction and thus formation of the second spirocenter.⁶¹ Therefore stepwise cyclization was necessitated. Conformers **847a** and **847b** both give rise to spiroketal **848** which benefits from maximization of anomeric effects in spite of the axial orientation of the methoxy group. Protecting group modification is followed by a second cyclization using iodobenzene diacetate-iodine to afford trioxadispiroketal **849** and **850** (58% and 20% yields respectively).

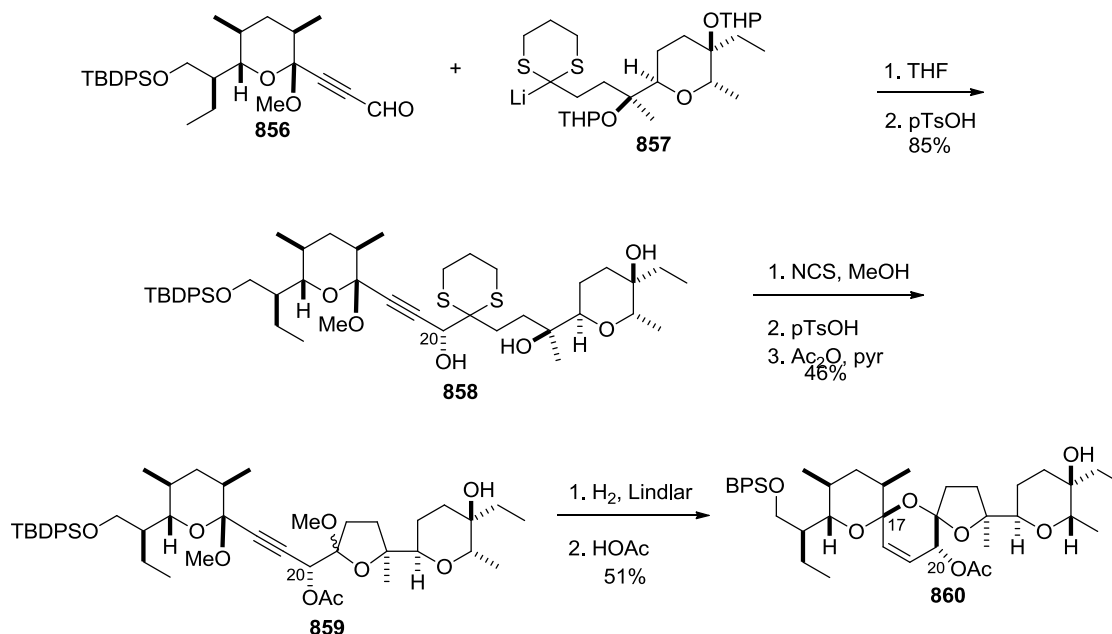
Brimble used a similar methodology to form the saturated (5,6,6)-bis-spiroketal systems **854** and **855** (Scheme 4.28).⁶² An allyl side chain was introduced to spiroketal **851** via stereocontrolled nucleophilic addition of allyltributyltin.⁶³ The allyl-substituted spiroketal was formed by Lewis acid-catalyzed oxonium ion generation, followed by nucleophilic addition of allyltributyltin to the carbonium ion intermediate. Hydroboration of spiroketal **852** was followed by treatment with iodobenzene diacetate and iodine to yield the *cis* (**854**) and *trans* (**855**) trioxadispiroketal in a 1.5:1 mixture respectively, favoring the isomer experiencing double anomeric effects. The oxidative cyclization conditions caused both rings to open, resulting in the mixture of isomers observed for this reaction.

Scheme 4.28



The first total synthesis of salinomycin was published by Kishi and involved umpolung coupling along with acid catalyzed trioxadispiroketal ring formation (Scheme 4.29).⁶⁴ The carbon skeleton was constructed by combining advanced aldehyde intermediate **856** with dithiane **857**. Alcohol deprotection and separation of the C₂₀ isomers yielded bis-tetrahydropyran intermediate **858** in 85% yield. Removal of the dithiane and acid catalyzed cyclization of the resulting ketone gave acetal **859**. The newly formed tetrahydrofuran ring, containing an alkyne, was reduced to the corresponding *cis* olefin, and then selectively converted into the trioxadispiroketal **860** isomer. This work was the first to demonstrate the feasibility of alkyne cyclization to form bis-spiroketals.

Scheme 4.29

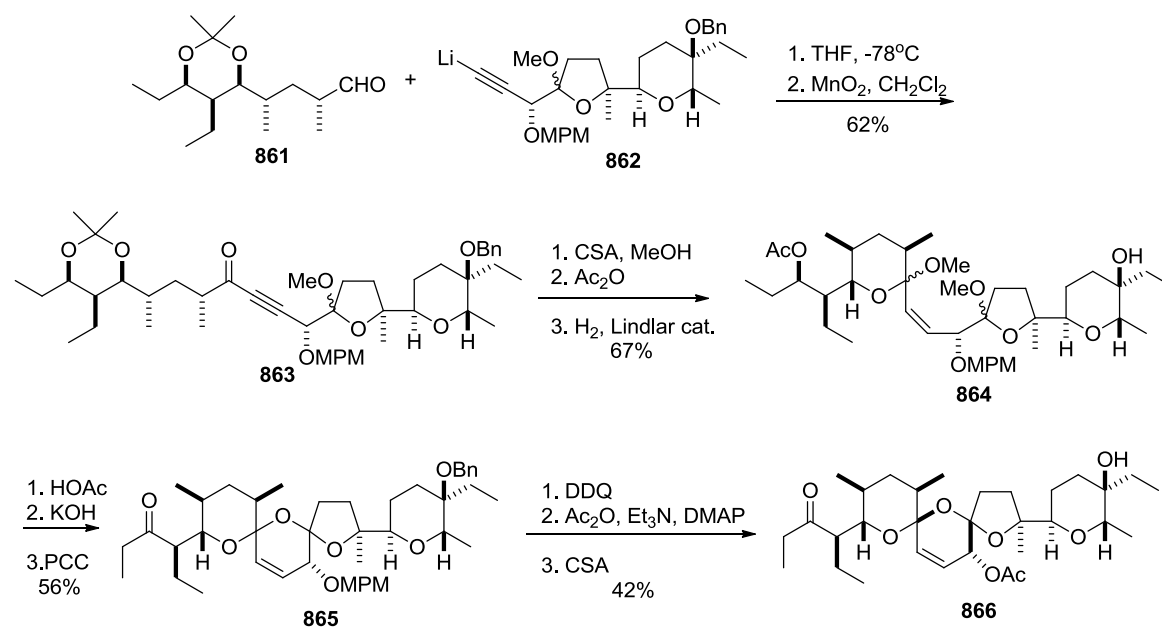


The bis-spiroketal formed is a C₁₇ epimer of the naturally occurring salinomycin and narisin, however, isomerization to the correct isomer readily occurs in a late stage synthesis. Although it is not precisely known, it is assumed that the free C₂₀ hydroxy substituent is key in creating the correct natural product stereochemistry. In fact there exist so many substituents off

of the trioxadispiroketal ring system of salinomycin that minimization of steric interactions rather than maximization of anomeric effects generally directs formation of the major isomer.

Yonemitsu's formal synthesis of salinomycin is similar to the Kishi approach. In this case the carbon skeleton is forged by addition of an alkyne nucleophile **862** to aldehyde **861** (Scheme 4.30).⁶⁵ Manganese dioxide oxidation was followed by acid catalyzed cyclization to

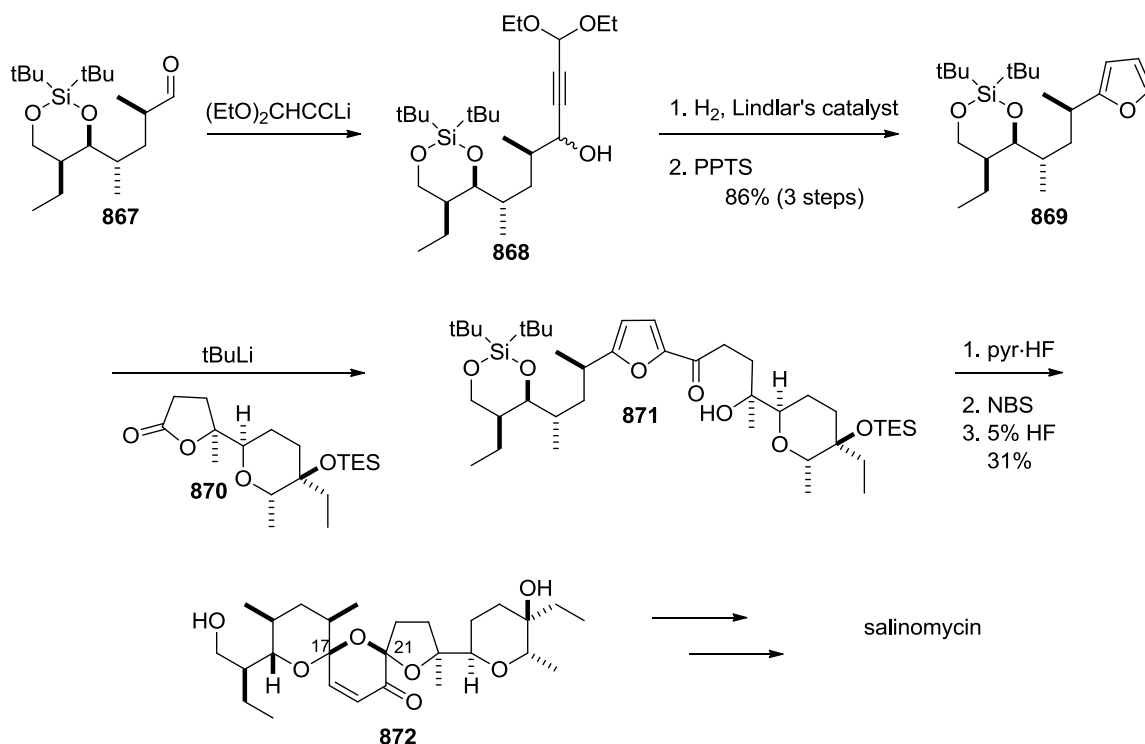
Scheme 4.30



form the tetrahydropyran ring of intermediate **864**. Protecting group manipulation and alkyne reduction led to the trioxadispiroketal precursor. Like Kishi, Yonemitsu cyclized the bis-tetrahydropyranyl tetrahydrofuran ring system with acetic acid, which produced three trioxadispiroketal isomers (1.8:1.4:1.0) about the C₁₃ and C₁₇ stereocenters. Subsequent oxidation of the isomer mixture produced bis-spiroketals **865**. Protecting group manipulations and re-subjection of the mixture to acidic conditions led to formation of trioxadispiroketal **866** as a single isomer. This work represented a formal synthesis of salinomycin.

Brown's synthesis of salinomycin was based on the Perron model study,⁶⁶ whereby the trioxadispiroketal is constructed by oxidation and cyclization of the corresponding furan (Scheme 4.31).⁶⁷ Furan **869** was synthesized from aldehyde **867** in three steps: addition, partial

Scheme 4.31



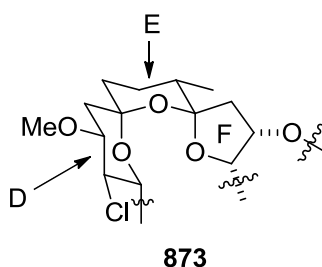
reduction of alkyne, and acid promoted aromatization. Furan **869** was subsequently metallated and added to lactone **870** to yield ketone **871**. Diol deprotection, oxidative rearrangement, and thermodynamic equilibration of the 2-acyl furan provided trioxadispiroketal **872** as the major isomer along with the C₂₁ epimer, in a 3:1 ratio respectively. The major trioxadispiroketal formed, **872**, is epimeric to salinomycin at the C₁₇ and C₂₁ stereocenters. As in the Kishi⁶⁶ case, late stage isomerization of the bis-spiroketal under acidic conditions successfully led to the natural product after a number of manipulations.

Spirastrellolide A **376** (Figure 4.4) is a trioxadispiroketal-containing natural product that has sparked more recent interest. A number of groups have worked toward the synthesis of this

natural product including Hsung,⁶⁸ Debrabander,⁶⁹ Smith,⁷⁰ Phillips,⁷¹ and Chandrasekhar.⁷² Few, however, have tackled the trioxadispiroketal-containing northern fragment. The Paterson,⁷³ Forsythe,⁷⁴ and Fürstner⁷⁵ groups have all reported efforts towards this end.

Stabilization of the trioxadispiroketal unit of spirastrellolide A is derived from two factors, a double anomeric effect, whereby all the ring oxygens are oriented axially to one another, and minimization of steric interactions, arising from an all equatorial arrangement of substituents. Therefore the conformation of the three-ring system is easy to predict, as Figure 4.10 illustrates, and thermodynamic spiroketalization processes can be expected to produce the

Figure 4.10

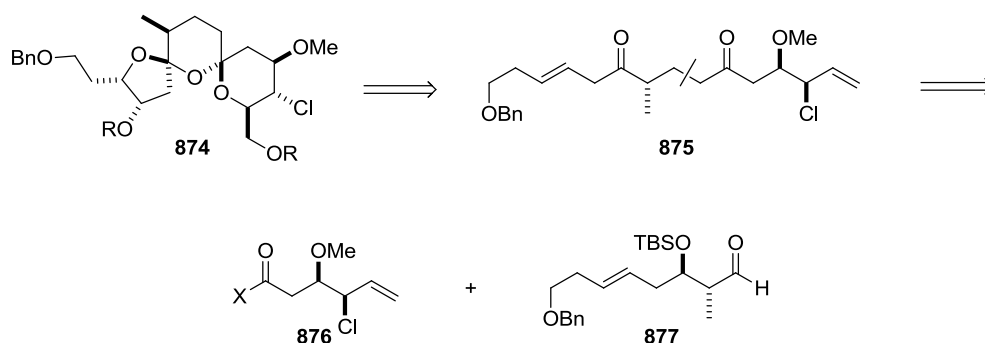


desired outcome. Most researchers took advantage of this observation in approaches to the bis-spiroketal unit of spirastrellolide. Though all three research groups set the C₃₆ stereocenter prior to spiroketalization, in theory the stereochemistry at that position can be set by epimerization under thermodynamic conditions. One problem that these groups faced toward the synthesis of this fragment was the tetrahydrofuran's propensity toward elimination. In addition, research groups at that time had to design synthetic routes compatible with the unknown relative stereochemistry between the C₃-C₇, C₉-C₂₄, and C₂₇-C₃₈ stereoclusters.

Paterson first published work towards the synthesis of the trioxadispiroketal moiety or “northern fragment” of spirastrellolide A in 2005.⁷⁶ The Paterson synthesis of the fragment developed in three iterations, where each successive approach either improved the overall yield

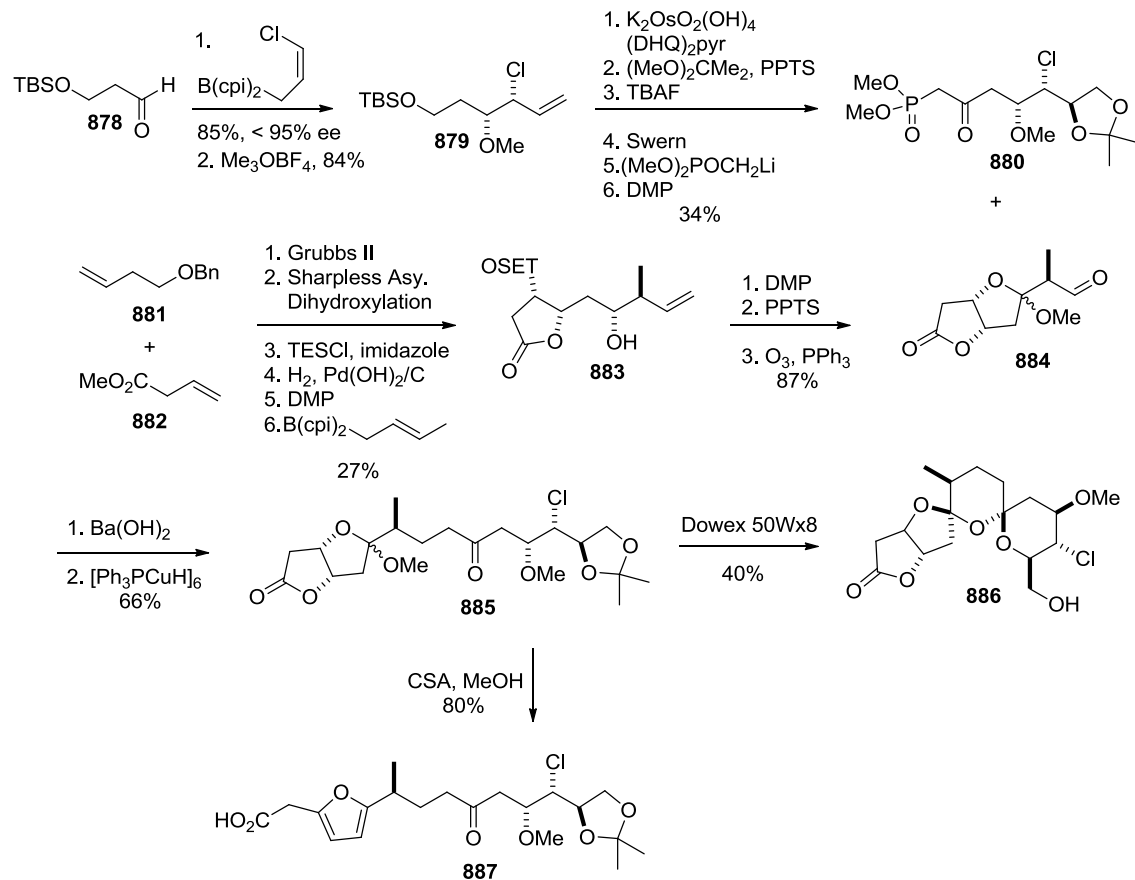
or the scalability of the process for application to the total synthesis. The general approach by Paterson is summarized in Scheme 4.32. The trioxadispiroketal is formed from the acid catalyzed cyclization of a multi-oxygenated substrate created from the Sharpless asymmetric dihydroxylation of precursor **875**. These three routes differed mainly in the sequence of dihydroxylation with other synthetic steps, the final route employing this oxidation in the last step. The carbon skeleton of the bis-spiroketal precursor was formed from either aldol or Horner-Wadsworth-Emmons addition of substrates with functionalities like chloride **876** and aldehyde **877**.

Scheme 4.32



The original Paterson route is outlined in Scheme 4.33 and features the Horner-Wadsworth-Emmons reaction of a bicyclic aldehyde **884** to prepare the spiroketal backbone. Manufacture of phosphonate **880** began from known aldehyde **878**. Oehlschlager-Brown chloroallylation and methylation of the resulting alcohol afforded olefin **879** in > 95% ee.⁷⁷ This efficient method for the challenging introduction of chlorine was used in all of Paterson's syntheses of Spirastrellolide A. Sharpless asymmetric dihydroxylation⁷⁸ of olefin **879** was followed by diol protection, silyl ether cleavage, and subsequent Swern oxidation to afford the corresponding aldehyde. Subsequent addition of lithiated methylene phosphonate and oxidation with Dess-Martin periodionane gave the β -ketophosphonate **880** thereafter.

Scheme 4.33



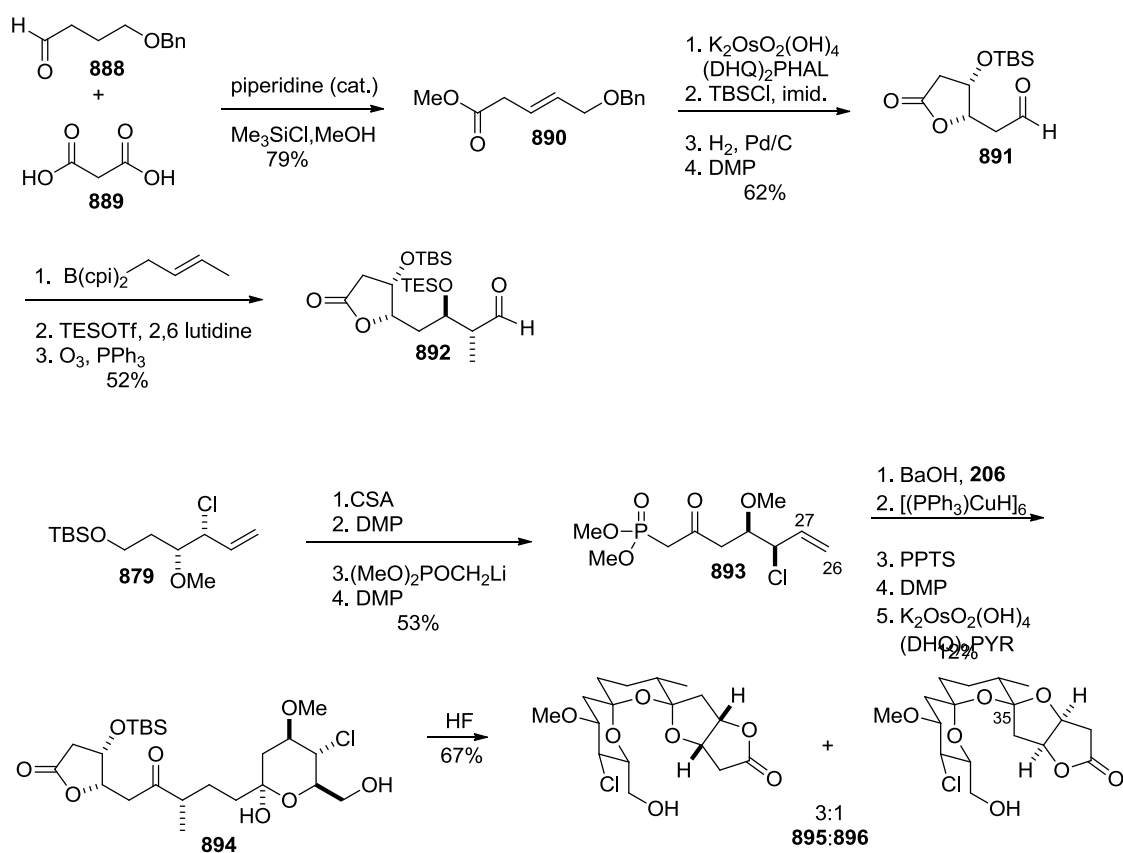
The synthesis of intermediate **884** began with a cross-metathesis of olefins **881** and **882** using Grubbs second generation catalyst.⁷⁹ The resulting (*E*)-olefin was subjected to asymmetric dihydroxylation (97:3 dr) with concomitant cyclization to form the corresponding 5-membered lactone selectively. Protection of the secondary alcohol, removal of the benzyl-protecting group, and subsequent oxidation yielded an aldehyde that was transformed stereoselectively into alcohol **173** after Brown crotylation (95:5 dr).⁸⁰ Oxidation of the newly formed alcohol, acid catalyzed cyclization, and oxidative cleavage of the terminal olefin yielded desired aldehyde **884**.

Phosphonate **880** was deprotonated with barium hydroxide and coupled with aldehyde **884** via a Horner-Wadsworth-Emmons reaction. Reduction of the resulting olefin was problematic. Use of typical reduction conditions on the newly formed olefin, such as

hydrogenation over catalytic palladium on carbon, led to decomposition products. Therefore conjugate reduction conditions with Stryker's reagent,⁸¹ were employed for the formation of cyclization precursor **885**. From here, effective spiroketalization of ketone **885** was dependent on the choice of catalyst. Treatment of ketone **885** with Dowex resin yielded the desired trioxadispiroketal **886** in 40% yield, while use of stronger acids, such as CSA, resulted in formation of furan **887**.

Paterson designed a second synthesis toward the northern fragment of spirastrellolide A in hopes of alleviating the formation of furan **887** (Scheme 4.34).^{75b} The redesigned synthesis reversed the direction of acetalization from ring F → FED to ED → FED, while also

Scheme 4.34



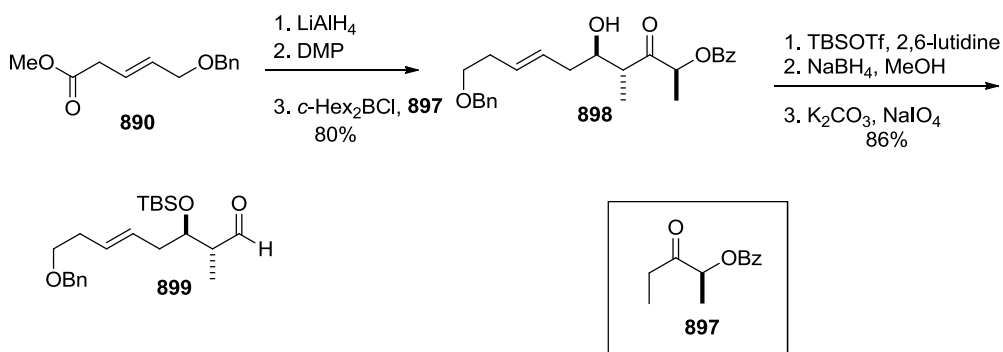
performing a late stage hydroxylation of the C_{26,27} olefin, thus eliminating the need for acetonide deprotection. The synthesis began with the coupling of aldehyde **888** and malonic acid **889** via a deconjugative Knoevenagel condensation to form the *E*-(β,γ)-unsaturated ester **890**.⁸² This method proved to be more efficient for the synthesis of ester **890** than the corresponding cross-metathesis used in the first generation synthesis. Lactone **891** was then prepared from ester **890** through a route similar to that in the first synthesis. Brown crotylation of lactone **891**, protection of the newly formed alcohol, and oxidative cleavage of the olefin yielded aldehyde **892**.

Phosphonate **183** was prepared in a manner similar to that described in the first Paterson route, except that the dihydroxylation of the terminal olefin was deferred until later in the synthesis. Silyl ether cleavage of olefin **879**, an intermediate formed in the first generation synthesis, was followed by oxidation, phosphonate addition, and subsequent oxidation to yield phosphonate **893**. Phosphonate **893** and aldehyde **892** were coupled in a Horner-Wadsworth-Emmons reaction and reduced by Stryker's reagent. Removal of the TES-group was then followed by Dess Martin oxidation to provide the corresponding ketone. Asymmetric dihydroxylation of the terminal double bond was accompanied by cyclization of the D ring to afford tetrahydropyran **894**. Subsequent silyl cleavage and concomitant cyclization resulted in the formation of the desired trioxadispiroketal **895** along with a C₃₅ epimer **896**. Efforts to recycle epimer **896** resulted in elimination. The formation of the undesired epimer along with the inability to scale up this process led Paterson to adopt yet a third approach toward the trioxadispiroketal system (Scheme 4.35-4.36).

The final approach toward the northern fragment features an asymmetric aldol reaction to assemble key fragments as well as late stage bis-hydroxylation. The manufacture of aldehyde **189** began from a previously synthesized intermediate, the ester **180** (Scheme 4.35).

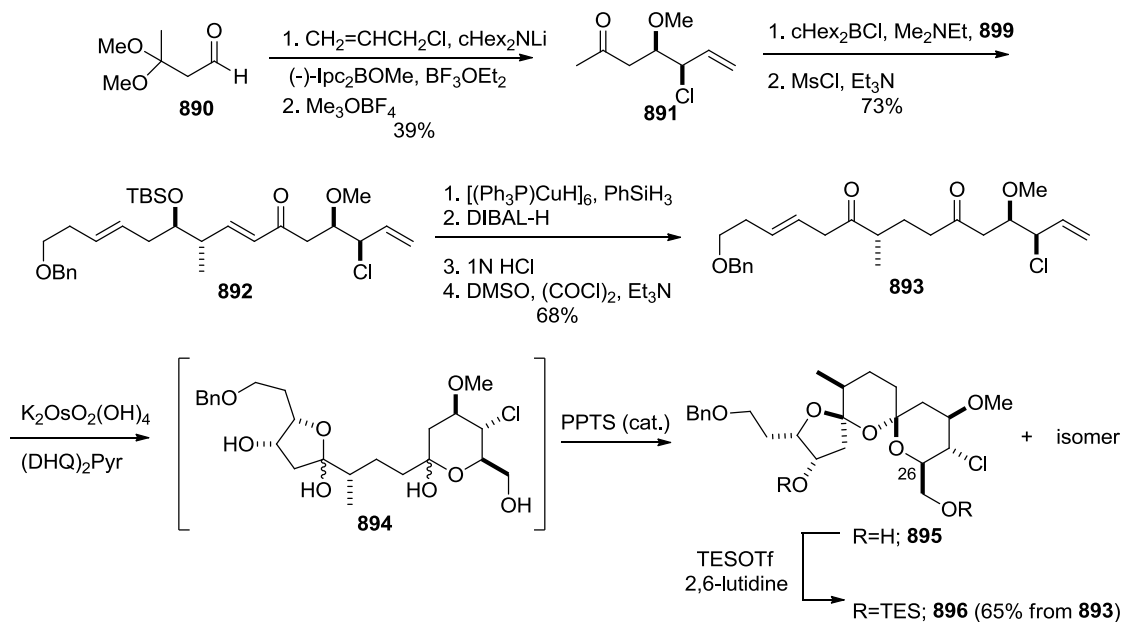
Manipulation of this intermediate to give the corresponding aldehyde was followed by an aldol reaction with ketone **187** to form the *anti*-aldol adduct **188** stereoselectively. Alcohol protection, reduction, and oxidative cleavage of the resulting diol then afforded aldehyde **189**.

Scheme 4.35



Formation of requisite chloroketone was again achieved by Oehlschlager-Brown chloroallylation, followed by subsequent formation of the methyl ether (d.r. > 95:5, 92% ee) (Scheme 4.36). Ketone **191** was converted to the kinetic dicyclohexylboron enolate and added to

Scheme 4.36



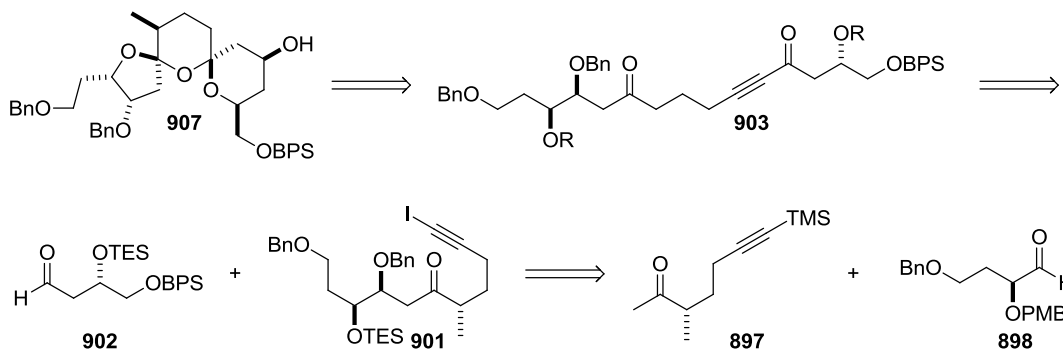
aldehyde **189** to form the aldol condensation product **192** upon elimination of the secondary alcohol. Conjugate reduction of the resulting enone using Stryker's reagent, silyl ether cleavage, and Swern oxidation gave the linear precursor **193** for spiroketalization.

A bis-asymmetric Sharpless epoxidation of **893**, the key step of the synthesis, afforded the partially cyclized intermediate **894**, which after treatment with PPTS gave the desired trioxadispiroketal **895** along with other isomers. Use of PPTS for this cyclization was essential because stronger acids such as CSA or HCl again resulted in competitive furan formation. Because the spiroketal isomers were unstable to chromatography, they were converted to the corresponding triethylsilyl ethers prior to purification. Separation of the TES-protected bis-spiroketal **196** from other isomers was then successful. These minor isomers were successfully recycled by re-subjection to PPTS and subsequent TES-diol protection to afford bis-spiroketal **896**. After one recycle, trioxadispiroketal **896** was formed in 65% from ketone **893**.

Paterson's final synthesis of the northern fragment differed from his first two in several ways. The lactone moiety used to set the stereochemistry at C₃₇ and C₃₈ in the first two syntheses was avoided in the third generation to reduce the incidence of furan formation. The new method also used reactions that were scaleable, a feature essential for the total synthesis of this large and complex molecule. Additionally, the asymmetric dihydroxylation and subsequent cyclization were performed concurrently, and at a late stage in the synthesis. This modification resulted in an efficient and elegant end to the trioxadispiroketal core. Overall the best Paterson synthesis of spirastrellolide A (route 3) was realized over 16 linear steps in a reported 18% yield. Unfortunately this process required that unwanted bis-spiroketal isomers be recycled to maximize the overall yield of the northern spirastrellolide fragment.

Forsyth was one of the first authors to report work toward the DEF ring system of spirastrellolide A.⁷⁷ This approach included a chelation-controlled Mukiyama aldol reaction, a Nozaki-Hiyama-Kishi⁸³ coupling to assemble key fragments, and a thermodynamic bis-intramolecular hetero-Michael addition (Scheme 4.37). Synthesis of the trioxadispiroketal began

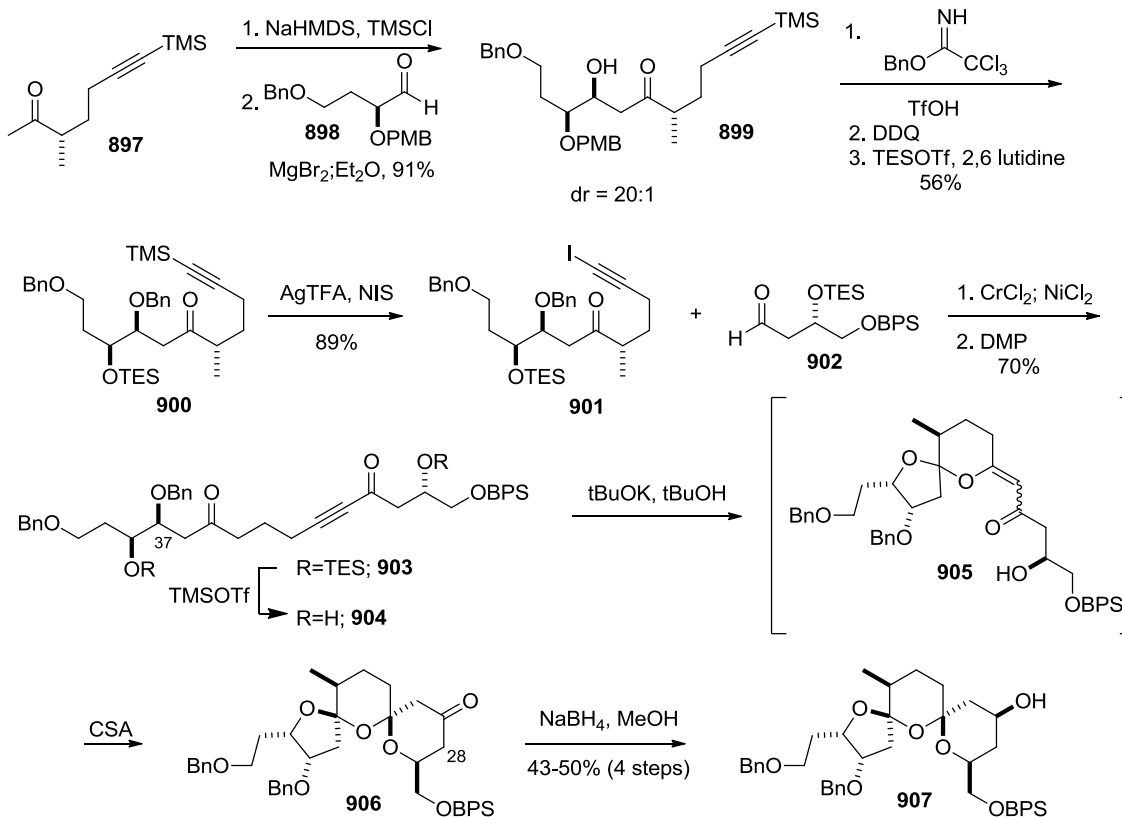
Scheme 4.37



with a selective Mukiyama aldol coupling between ketone **897** and aldehyde **898** (20:1 dr) (Scheme 4.38). Protecting group manipulations of the aldol adduct **899** then yielded the ketone **900**, which was converted to the alkynyl iodide **901**. Nozaki-Hiyama-Kishi coupling of this iodide with aldehyde **902** and subsequent oxidation gave ketone **903**.⁸⁴ Removal of the TES-protecting groups gave the linear backbone **904**, which was poised for spirocyclization.

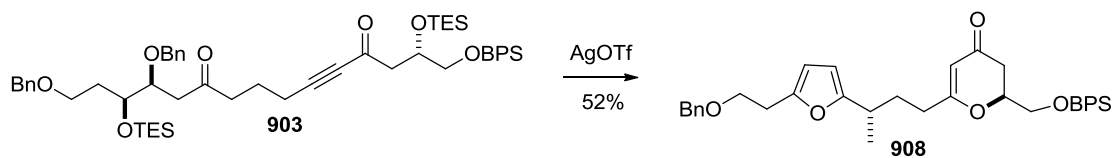
Cyclization of alcohol **904** was initiated under base-catalyzed conditions, followed by treatment with CSA. The resulting ketone **906** was highly unstable, however, and was therefore reduced to the more stable corresponding alcohol **907**, which proved to be less labile. The introduction of the C₂₈ chlorine substituent, present on spirastrellolide A, was intended through selective α -keto chlorination of the spirocyclic ketone, which was no longer possible. Therefore the sequence was modified so as to introduce the chlorine at an early stage in the synthesis.

Scheme 4.38



It is interesting to note that spirocyclization of alkyne **904** under acidic conditions was problematic, and resulted in elimination of the C₃₇ oxygen functionality regardless of the protecting groups utilized. Activation of alkyne **904** using metal salts such as AgOTf led to one of two results; a competing single hetero-Michael addition and β -elimination or no reaction at all (Scheme 4.39). So after base catalyzed spiroketalization to form spiroketal intermediate **905**,

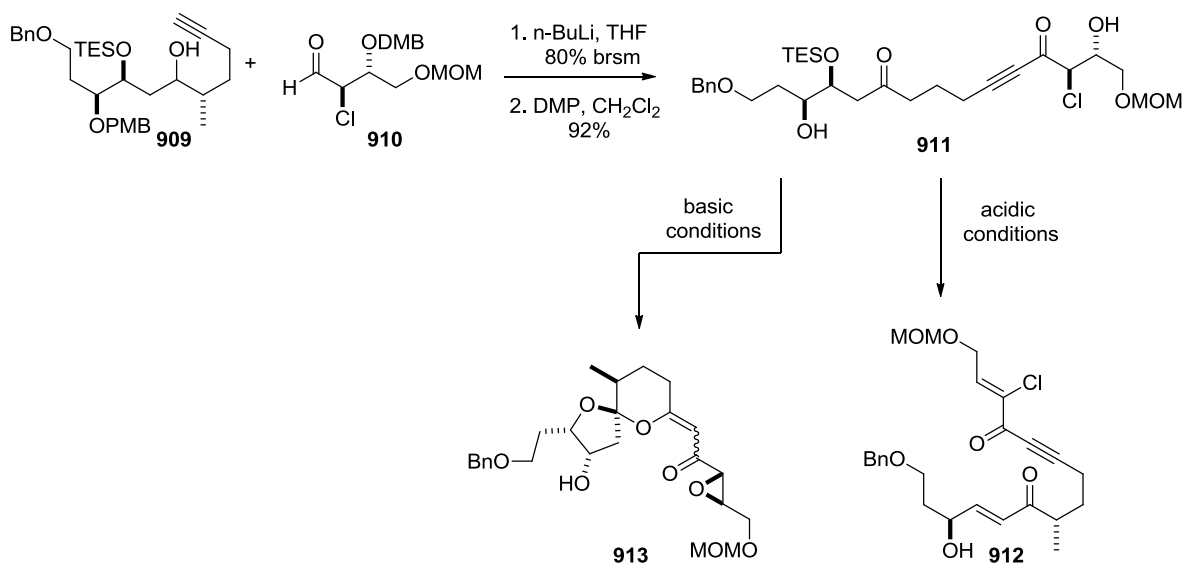
Scheme 4.39



CSA was used to induce the second cyclization to form the unstable bis-spiroketal **906** that was then reduced to the alcohol.

Forsyth's second attempt toward the trioxadispiroketal of spirastrellolide A involved installation of the chlorine substituent at an early stage (Scheme 4.40). Though incorporation of

Scheme 4.40

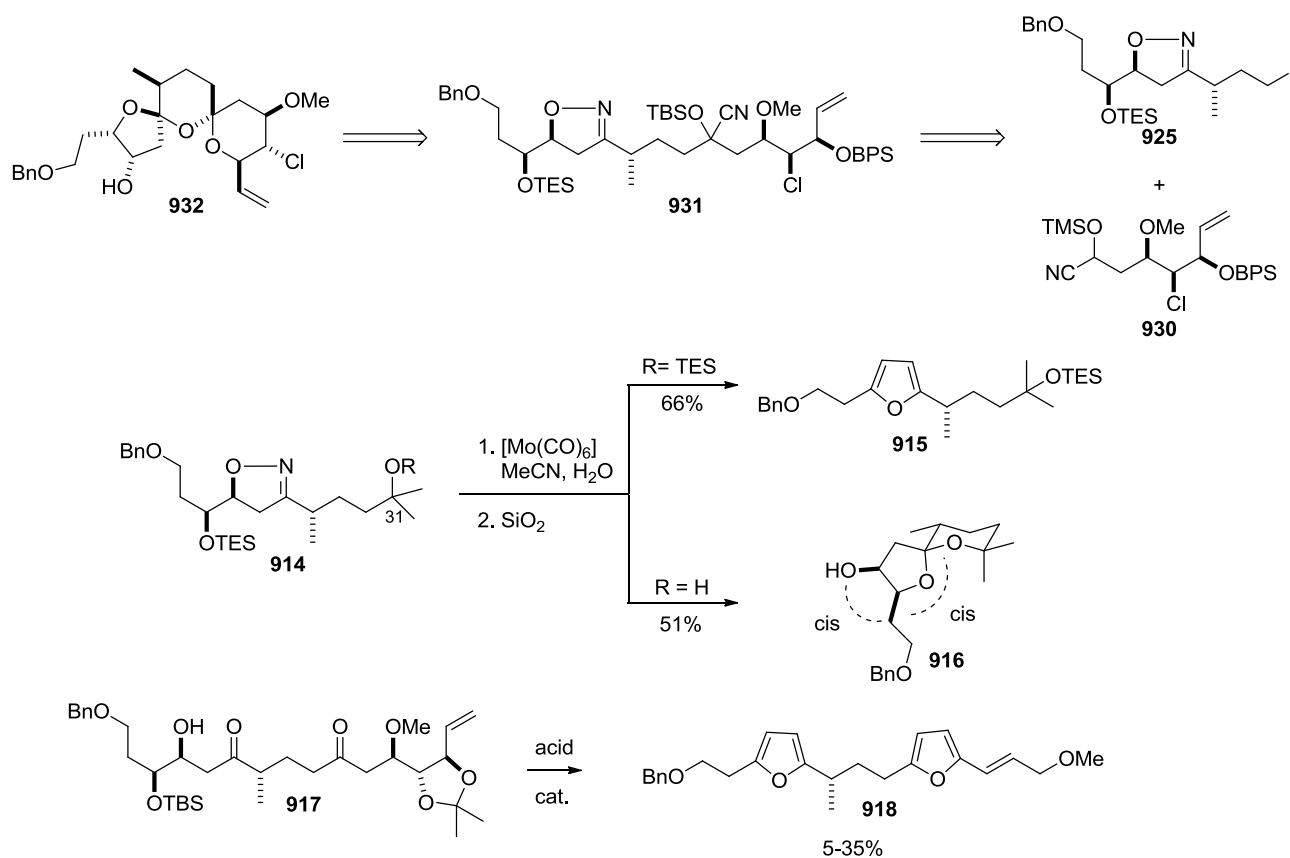


this functionality into the linear precursor **911** was straightforward, the presence of the chlorine substituent during spiroketalization led to either elimination product **912** in the presence of acid or epoxide-containing spiroketal **913** with base. While a successful synthesis of the spirastrellolide A spiroketal was not realized, Forsyth demonstrated that the double intramolecular hetero-Michael addition was an effective method for manufacture of DEF analogs of spirastrellolide A that lack a chlorinated substituent.

Fürstner's synthesis of C₂₇-C₃₈ of spirastrellolide A differed from those of Paterson and Forsyth in that kinetic rather than thermodynamic spiroketalization conditions were used to form

the trioxadispiroketal.⁷⁸ Fürstner anticipated spirocyclization of a ketoisoxazoline **931** to form the bis-spiroketal moiety **932** (Scheme 4.41). The synthesis of the ketoisoxazoline **931** was in turn envisioned through the umpolung coupling of isoxazoline **925** with nitrile **930**. Model studies on a simpler substrate suggested that thermo spirocyclization would result in unwanted byproducts. This work demonstrated that thermodynamic spiroketalization of the 2-isoxazoline **914** resulted in aromatization to give furan **915** upon extensive equilibration (Scheme 4.41).

Scheme 4.41

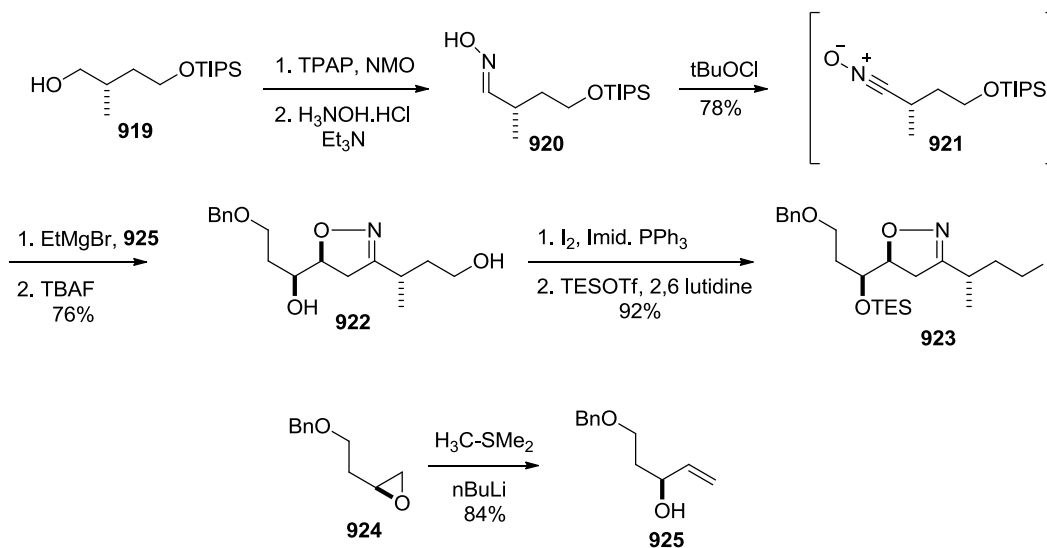


Direct cyclization of isoxazoline **914** provided either furan **915** or spiroketal **916**, depending on the availability of the C_{31} alcohol toward immediate cyclization. When the C_{31} alcohol is unprotected, spirocyclization occurs cleanly to give the EF ring system **916**. However,

when the C₃₁ alcohol is TES-protected, aromatization is favored resulting in formation of furan **915**. Presumably, aromatization occurred to avoid the transannular strain that develops within the tetrahydrofuran system due to the all-*cis* configuration. Likewise, acid catalyzed cyclization of the extended diketone **917** in which all alcohols that are participating in the spirocyclization are protected, led solely to the bis-furan byproduct **918**. These model studies showed that furan byproduct formation occurs when the C₃₁ alcohol is unavailable towards cyclization. To avoid furan formation, the synthesis of spirastrellolide A was carefully planned around proper protecting group cleavage to promote spiroketal formation and avoid production of furan byproducts through equilibration.

Fürstner's forward synthesis is outlined in Schemes 4.42 and 4.43. Key steps include [1,3]-dipolar cycloaddition, umpolung coupling, and kinetic spiroketalization. The synthesis of isoxozoline **923** was initiated from monoprotected diol **919** (Scheme 4.42). Diol **919** was

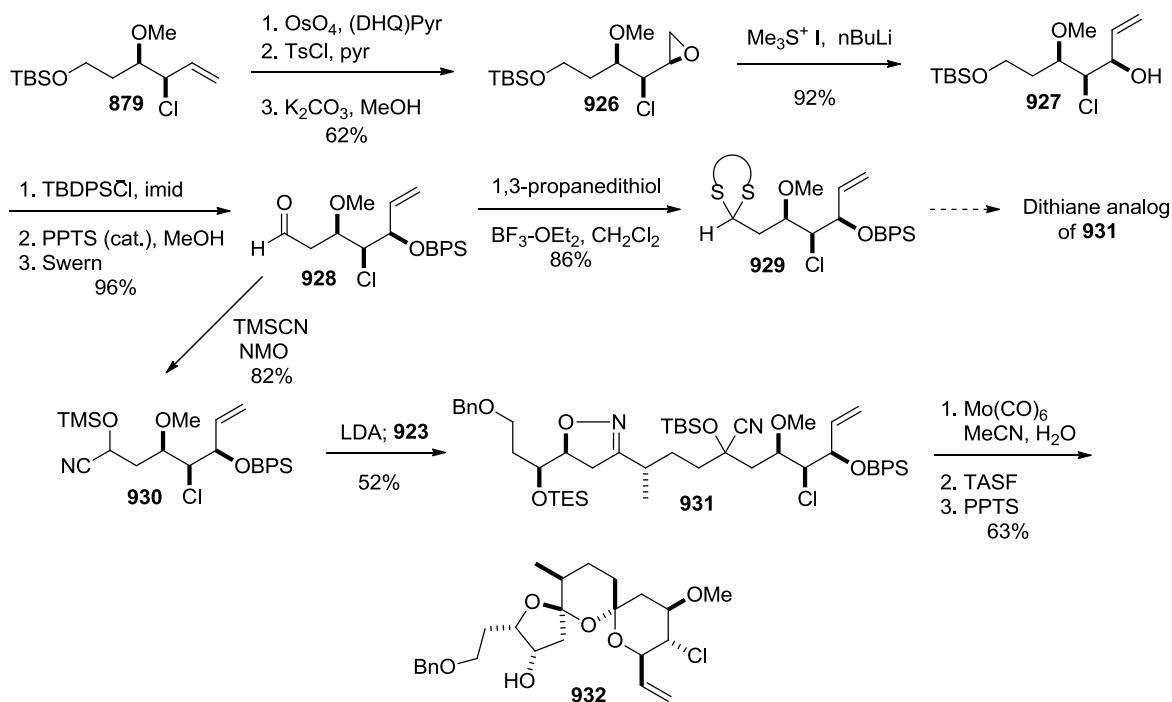
Scheme 4.42



converted to oxime **920** by oxidation and reaction with ammonium hydroxide. The corresponding nitrile oxide **921** reacts with enantiopure allylic alcohol **925** to give isoxazoline **922** in 76% yield. The Kanamasa⁸⁵ protocol selectively formed the desired stereoisomer exclusively. The preparation of isoxazoline **923** was completed by selective iodination of the primary alcohol and protection of the secondary alcohol as the TES ether. This intermediate was later used for preparation of the linear spirocyclization precursor. The allylic alcohol used in the [3+2] dipolar cycloaddition was prepared by addition of dimethylsulfonium methylide to epoxide **924**, which was readily available by hydrolytic kinetic resolution.

The preparation of bis-spiroketal **932** was then completed as shown in Scheme 4.43. Like Paterson, Fürstner began this sequence from chloroether **879**, which was synthesized in two steps from aldehyde **878** (Scheme 4.33). Asymmetric dihydroxylation, followed by selective

Scheme 4.43



tosylation of the primary alcohol afforded the terminal epoxide **926** upon treatment with base. Subsequent homologation with dimethylsulfonium methylide gave the allylic alcohol **927**. This transformation was not a trivial due to the potential for competing chloride displacement. In the end, the desired allylic alcohol was prepared in four steps and 57% yield from chloride **879**. Protecting group manipulations and subsequent oxidation then provided aldehyde **928**.

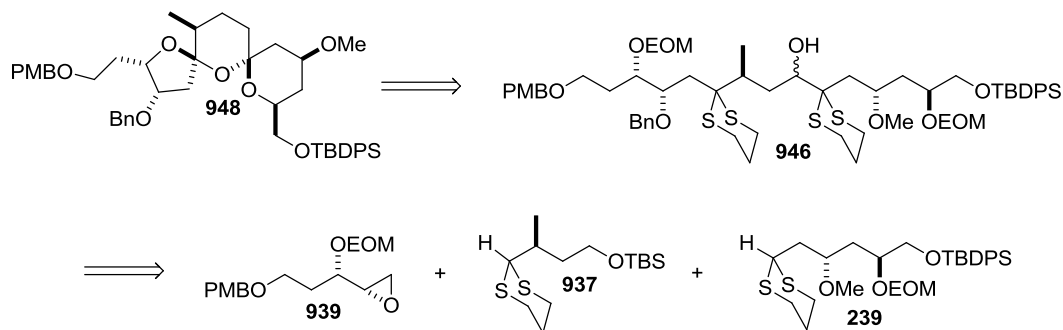
At this point an umpolung coupling was envisioned between aldehyde **928** and iodide **923**. After conversion of aldehyde **928** to dithiane **929**, deprotonation under a number of different conditions proved difficult. Therefore, this substrate was abandoned and aldehyde **928** was converted instead to cyanohydrin **930**. This intermediate could be effectively deprotonated with LDA and subsequently alkylated with iodide **923** to give the linear cyclization precursor. Cleavage of the isoxazoline moiety, global deprotection, and subsequent, kinetic cyclization (in the presence of PPTS) provided the desired trioxadispiroketal **932** along with two other isomers (4.1:1.7:1 dr respectively). No furan-containing products were isolated.

This sequence effectively produced the DEF-ring system of spirastrellolide A in a highly convergent manner. The desired bis-spiroketal was formed in 15 linear steps and 11% overall yield from aldehyde **878**. This approach differed from those previous in both the use of isoxazoline intermediates and a kinetic spiroketalization process. The trioxadispiroketal thus prepared was later used by Fürstner in the synthesis of spirastrellolide G.⁸⁶

More recently Brimble devised a synthesis for the northern fragment of spirastrellolide B, which differs from spirastrellolide A in that it does not contain a chlorine at C₂₈.⁸⁷ This lack of functionality results in a somewhat simplified synthesis compared to the previous work toward spirastrellolide A. Brimble's strategy involved formation of the carbon skeleton **946** through a

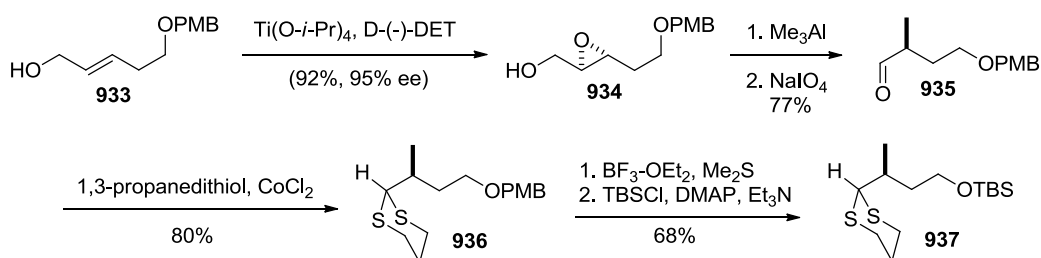
series of dithiane couplings (Scheme 4.44). The final spiroketalization was achieved in the presence of HgCl_2 under thermodynamic conditions.

Scheme 4.44



Dithiane **937** was prepared in six steps from the known allyl alcohol **933** (Scheme 4.45). Sharpless asymmetric epoxidation, regioselective ring-opening with trimethyl-aluminum,⁸⁸ and oxidative cleavage of the 1,2-diol produced aldehyde **935**. Formation of the dithiane **936** and protecting group manipulations subsequently yielded dithiane **937**.

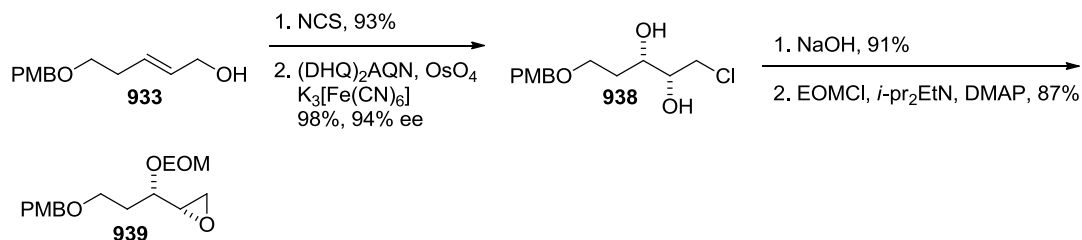
Scheme 4.45



The synthesis of epoxide **939** also began from allyl alcohol **933** (Scheme 4.46). Alkene **933** was transformed into diol **938** by conversion of the alcohol to the corresponding chloride and Sharpless dihydroxylation. Intramolecular epoxidation followed by protection of the

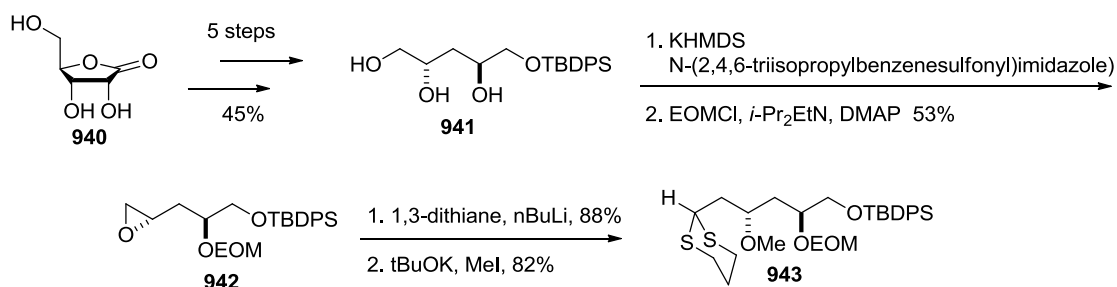
remaining secondary alcohol as the ethoxymethyl (EOM) ether gave the enantiomerically enriched epoxide **939** in 78% overall yield.

Scheme 4.46



The third intermediate, dithiane **943** was prepared in four steps from triol **941**, which is readily available from D-(+)-ribonic acid γ -lactone **940** (Scheme 4.47).⁸⁹ In this sequence triol **941** was transformed to epoxide **942** by conversion of the primary alcohol to the substituted sulfone, which underwent internal displacement by the adjacent free alcohol, and protection of the remaining hydroxyl group. In turn this compound was transformed to dithiane **943** after addition of lithiated 1,3-dithiane and methyl ether formation.

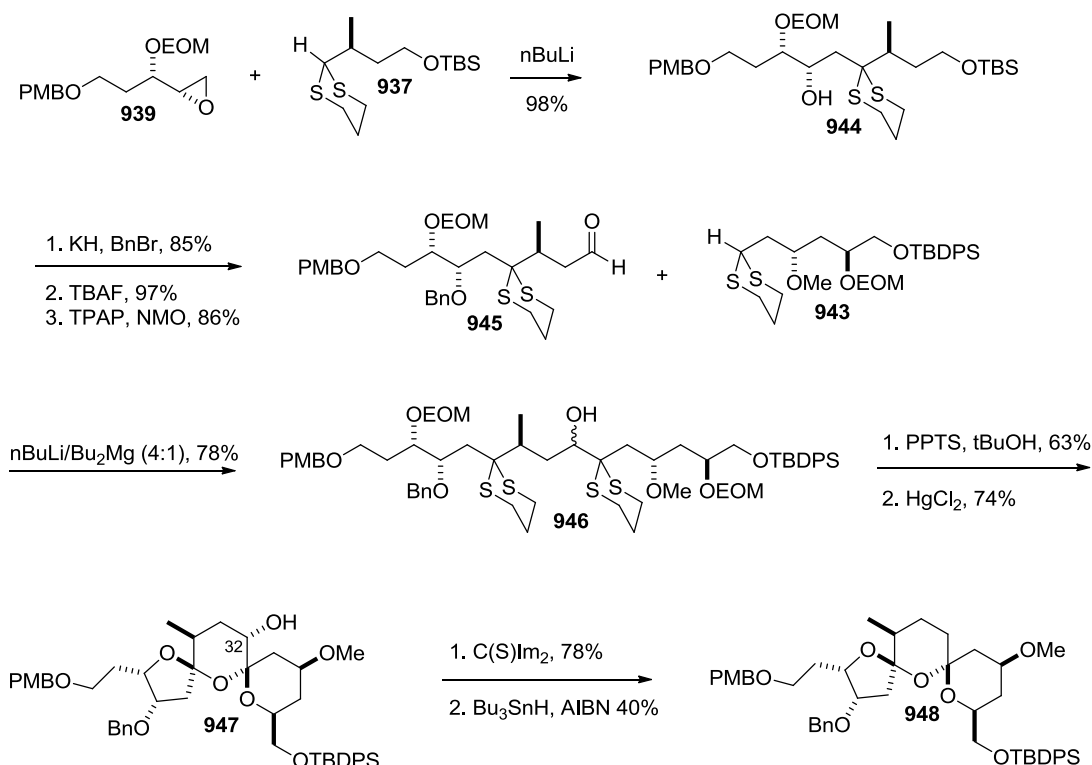
Scheme 4.47



With the three key intermediates in hand, unit coupling began with deprotonation of dithiane **937** followed by addition of epoxide **939** (Scheme 4.48). Protection of the resulting

secondary alcohol **944**, deprotection of the primary silyl ether, and TPAP oxidation then yielded aldehyde **945**, which was combined with the deprotonated dithiane **943** to give alcohol **946**. Acidic cleavage of the EOM groups gave an intermediate triol which after subsequent dithiane removal and concomitant cyclization yielded the bis-spiroketal **947** as a single diastereomer. Conversion of this compound to the DEF-ring of spirastrellolide B was then achieved through a modified Barton deoxygenation at C₃₂. Overall, the bis-spiroketal portion of spirastrellolide B was prepared in 15 steps from the known allyl alcohol **933** in 5.7 % yield. This process benefited from use of the same starting material for two of the three required intermediates and used simple dithiane couplings to construct the carbon skeleton of the bis-spiroketal **948**.

Scheme 4.48



In general, the preparation of trioxadispiroketal involves acid catalyzed/promoted cyclizations of multioxygenated precursors. Such methods have been used towards the synthesis of trioxadispiroketal portions of the pinnatoxins, salinomycins, and spirastrellolides as well as for the preparation of (5,5,5)- and (6,6,6)-bis-spiroketal systems. Although less popular, Norrish type II cleavage and oxidative cyclization with hypiodite have also been used successfully in the synthesis of (5,6,5)-trioxadispiroketal, and (5,6,6)- and (6,6,6)-bis-spiroketal systems respectively. Use of thermodynamic spiroketalization conditions yields predominantly the most stable isomers, which typically match the stereochemistry found in the natural product targets. Unlike previous groups, we envisioned the synthesis of trioxadispiroketal systems from the acid catalyzed spiroketalization of pyran precursors derived from the two directional carbonyl ene reaction of exocyclic enol ethers.

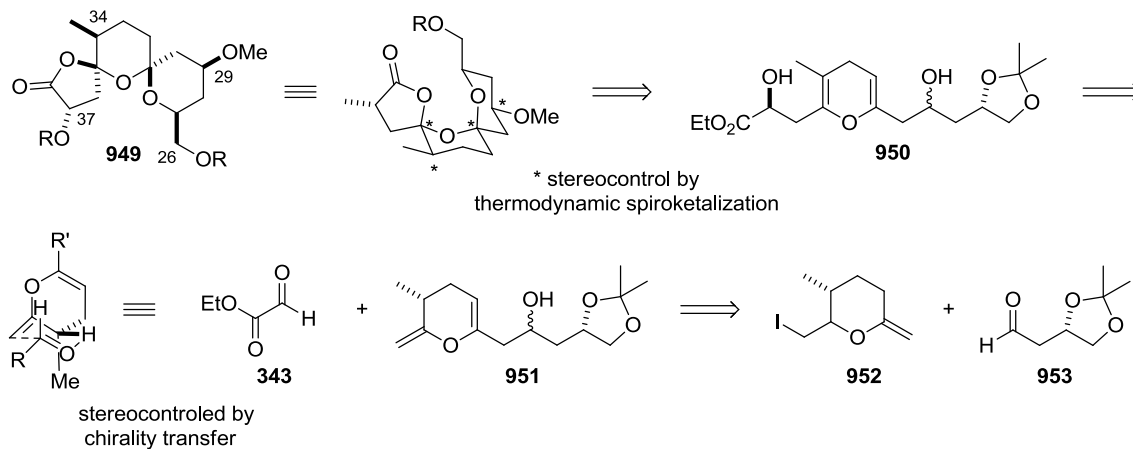
4.3 Results and Discussion

Carbonyl-Ene Approach to the Synthesis of Trioxadispiroketal

Our approach to *bis*- β -hydroxypyran and trioxadispiroketal synthesis builds from our success with the carbonyl-ene reaction of 2-methylenetetrahydropyrans and various enophiles as was discussed in Chapter 3 (Scheme 3.1).⁹⁰ The C₂₇-C₃₈ bis-spiroketal of the spirastrellolides, for example, was anticipated through the thermodynamic acid catalyzed cyclization of pyran **950** (Scheme 4.49). Pyran **950** could be synthesized by the two-directional carbonyl-ene reaction of aldehydes **343** and **953** with the bis-enol ether equivalent **952**. The spiroketal backbone **950** is anticipated through the carbonyl-ene reaction of the less reactive aldehyde **953** followed by elimination of the iodide and ene reaction of the newly generated enol ether with ethyl glyoxylate **343**. The reaction with ethyl glyoxylate **343** is predicted to yield stereo-enriched pyran **950** based on the chirality transfer studies outlined in Chapter 3. This step could

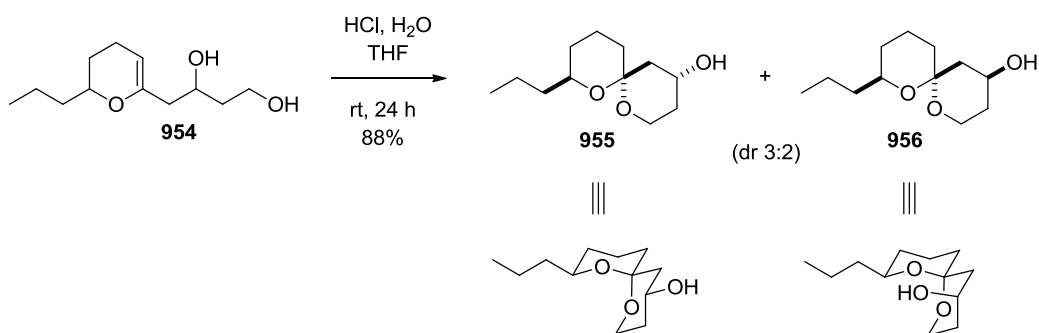
also be facilitated with chiral Lewis acid. Cyclization is predicted to yield spiroketal **949** where the C₂₉, C₃₁, C₃₄, and C₃₅ stereocenters are controlled by thermodynamic equilibration.

Scheme 4.49



Previous work in our lab has demonstrated the feasibility of controlling the stereochemistry at C₂₉ by equilibration (Scheme 4.50).⁹¹

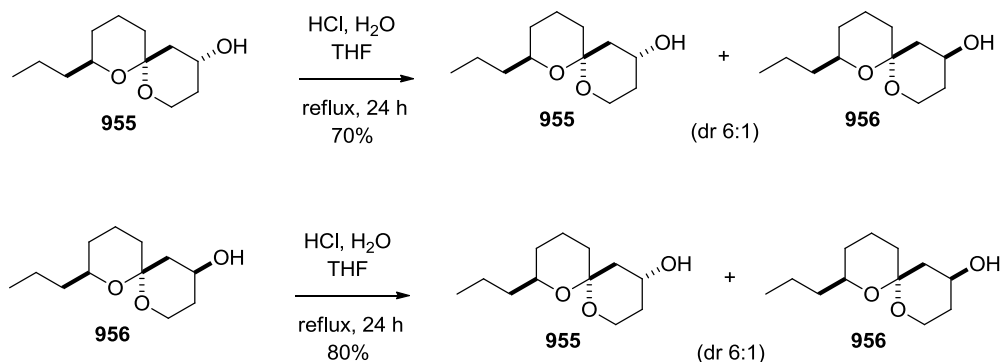
Scheme 4.50



When a 1:1 mixture of dihydropyrans **954** was subjected to aqueous hydrochloric acid in THF, the (6,6)-spiroketals **955** and **956** were formed in excellent yield as a 3:2 ratio of stereoisomers (Scheme 4.48). Upon chromatographic separation, the individual isomers were

resubjected to acid in refluxing THF (Scheme 4.51). In both cases, spiroketals **955** and **956** were obtained in a 6:1 ratio. Application of the equilibration conditions to both isomers demonstrated

Scheme 4.51

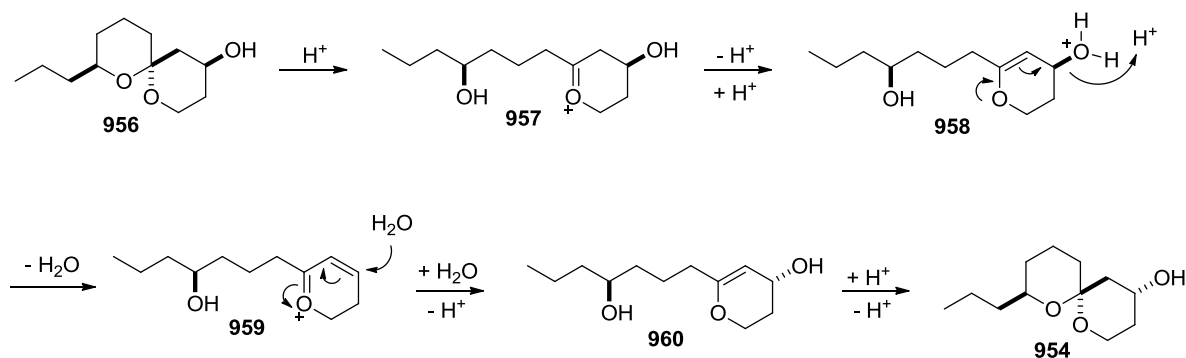


that Spiroketal **955** is lower in energy and thus the thermodynamic product. While both spiroketals **955** and **956** benefit from double anomeric stabilization and equatorial orientation of the propyl side chain, spiroketal **955** is further stabilized by the equatorial orientation of the hydroxy group. As previously discussed, free alcohols on spirocyclic systems typically prefer to be equatorial when cyclized under thermodynamic conditions in polar solvent. In these cases, the alcohol hydrogen-bonds preferentially to solvent rather than to the oxygen in the tetrahydropyran ring, increasing its effective steric bulk and preference for an equatorial orientation (Scheme 4.5 and 4.6). The conditions used for equilibration in this case involved dilute HCl in refluxing aqueous THF, which is unlikely to work for bis-spiroketalization of the labile pyran precursors. Instead equilibration of these systems could be carried out at room temperature over longer reaction times.

A mechanism for the interconversion of spiroketal **956** to **955** is shown in Scheme 4.52. This sequence has been previously proposed independently by both Smith⁹² and Mori in their

work toward the taleromycins.⁹³ Acid catalyzed ring-opening of spiroketal **956** results in formation of the oxonium ion **957**, which after double bond isomerization yields the enocyclic

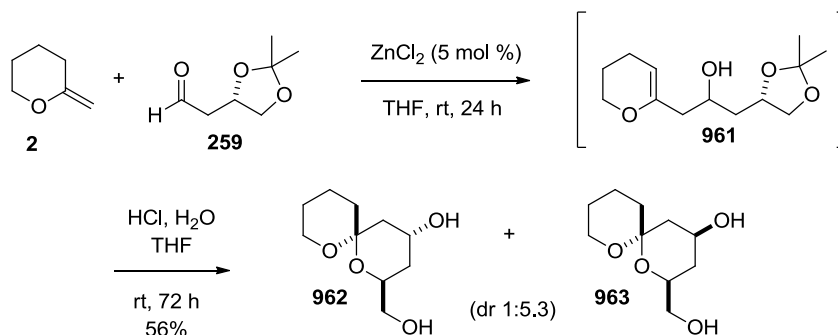
Scheme 4.52



enol ether **958**. Protonation of the C_4 hydroxyl group and loss of water then provides the conjugated oxonium intermediate **959**. A Michael-type addition of water from the opposite face (**960**) and spiroketalization then provides the thermodynamic spiroketal **954**.

A second (6,6)-spiroketal was prepared successfully using the carbonyl-ene /thermodynamic spiroketalization sequence to control the stereochemistry at C_3 (Scheme 4.53).

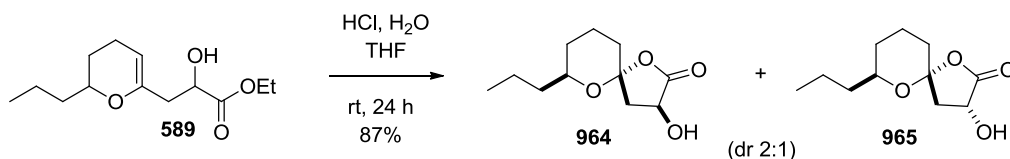
Scheme 4.53



This system more closely resembles that of the DE portion of the spirastrellolide northern fragment. By this method, 2-methylenetetrahydropyran **2** was combined with chiral aldehyde **259**, to provide ene adduct **960**, which was not purified, but treated directly with protic acid to give spiroketals **962** and **963**. Again, under thermodynamic conditions the equatorial hydroxy isomer **963** predominates.

Successive carbonyl-ene/spirocyclization reactions have also been demonstrated for the synthesis of (6,5)-spiroketal **264**, a system similar in structure to the EF spiroketal of spirastrellolide (Scheme 4.54).⁹⁷ Dihydropyran **589** was formed as a 1:1 mixture of diastereomers by reaction of the corresponding exocyclic enol ether **588** and ethyl glyoxylate **343** (Scheme 3.37). Upon treatment with acid, dihydropyran **589** cyclized to spiroketals **964** and **965** in a 2:1 ratio after 24 hours. In this case, the isomer most similar to the EF ring system of spirastrellolide A was favored. The bias for this selectivity is not known.

Scheme 4.54

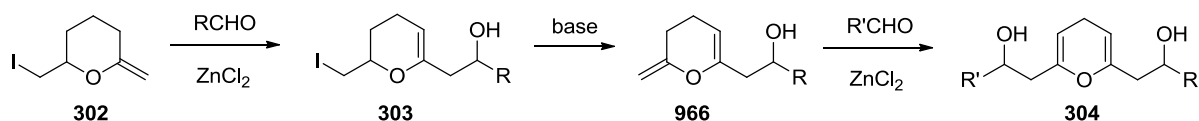


The successful preparation and equilibration of substituted (6,6)- and (6,5)-spiroketals using the carbonyl-ene/spirocyclization pathway described above support the use of this method in the preparation of the DEF-*bis*-spiroketal present in the northern fragment of the spirastrellolides. In particular, we sought to apply a two-directional carbonyl-ene methodology towards formation of *bis*- β -hydroxy pyrans, which in turn could be converted to trioxadispiroketals like that found in the spirastrellolides.

Synthesis of Bis- β -Hydroxypyrans

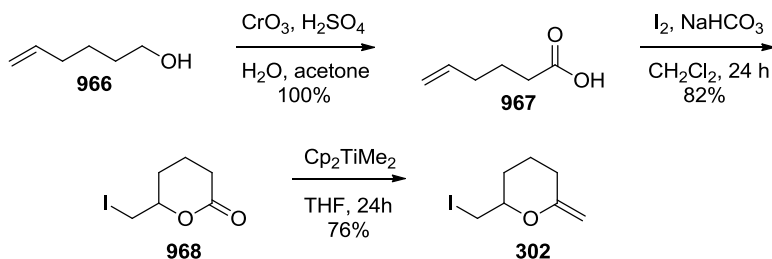
To achieve a synthesis of trioxadispiroketal, we first sought methods to create bis- β -hydroxypyrans, their envisioned precursors. The preparation of bis- β -hydroxypyrans is anticipated in a three-step sequence from 6-iodomethane-2-methylenetetrahydropyran **302** (Scheme 4.55). After the carbonyl-ene reaction between enol ether **302** and an aldehyde, base promoted elimination of the iodine results in compound **966**, which contains both endo and exo enol ethers. Prior work in the lab suggests the exocyclic enol ethers are more reactive than the endo, so therefore the second carbonyl-ene reaction is anticipated to react exclusively with the exo olefin to give the desired bis- β -hydroxylated pyran **304**.

Scheme 4.55



Efforts in this area began with the synthesis of the bis enol ether equivalent **302** from 5-hexen-1-ol as shown in Scheme 4.56. Jones oxidation⁹⁴ of the primary alcohol resulted in

Scheme 4.56



quantitative conversion to carboxylic acid **967**. Iodo-lactonization under slightly basic conditions afforded lactone **968**. Petasis olefination of lactone **968** then yielded enol ether **302** in good yield.

With enol ether **302** in hand, the next step was to explore the feasibility and limitations of the coupling methodology for the synthesis of bis- β -hydroxypyran. The first step in this sequence involved the carbonyl-ene reaction of exocyclic enol ether **302** with various enophiles. The results of these reactions are summarized in Table 4.4.

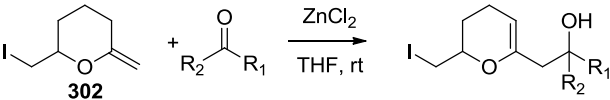
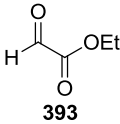
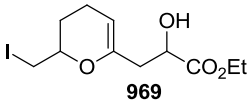
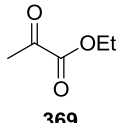
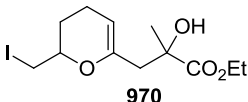
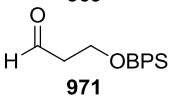
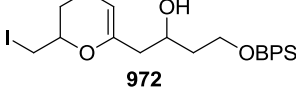
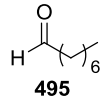
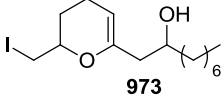
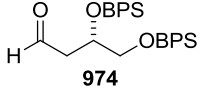
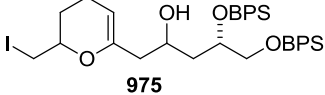
As shown, the reactivity of enol ether **302** varied with the structure of the carbonyl coupling partner. The reaction with ethyl glyoxylate **343** (Table 4.4, entry 1) produced the ene adduct **969** in good yield after 2 hours. Due to the inherent reactivity of this aldehyde, only 5 mole % of ZnCl_2 is required to catalyze this reaction in a short period of time. The carbonyl-ene reaction proved slower with non-activated aldehydes **972**, **973**, and **975** (entries 3, 4, and 5) and thus required higher catalyst loading and longer reaction times compared to the glyoxylate example. Similar results were obtained with the activated ketone **369** (entry 2). Nonetheless these substrates provided the desired ene products in good to excellent yields.

The carbonyl-ene reaction of exocyclic enol ether **302** was also compatible with activated ketone enophiles (Table 4.4, entry 2). Ethyl pyruvate **369** was combined with the enol ether to give ene adduct **970** in 66% yield. Although activated, the increased sterics inherent in the ketone slow the reaction, resulting in the need for longer reaction times and higher catalyst loading than the similar glyoxylate example (entry 1).

As with earlier work,⁹⁷ the presence of a substituent at C_6 on the enol ether had no influence on the stereoselectivity of the carbonyl-ene reaction. A 1:1 mixture of diastereomeric

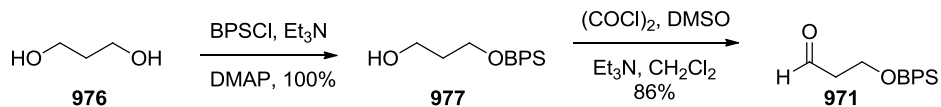
products resulted for entres 1-4. Ene adduct **975** was produced as a mixture of 4 diastereomers. In these circumstances, diastereoselectivity is of little consequence as one of the stereocenters will ultimately be destroyed in the next reaction.

Table 4.4: Carbonyl-Ene Reactions of 6-Iodomethyane-2-Methylenetetrahydropyran

<div style="text-align: center;">  </div>					
Entry	Enophile	Mol % ZnCl ₂	Time (h)	Product	Yield
1	 393	5	2	 969	84%
2	 369	20	24	 970	66%
3	 971	20	24	 972	99%
4	 495	20	11	 973	82%
5	 974	20	24	 975	76%

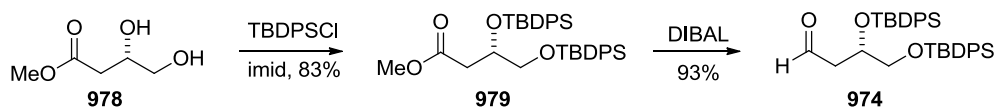
Ethyl glyoxylate **343**, octylaldehyde **495**, and ethyl pyruvate **369** are available from commercial sources, whereas aldehydes **971** and **974**⁹⁷ were prepared in a few synthetic steps from commercially available materials. Aldehyde **971** was prepared from the corresponding diol in two steps (Scheme 4.57). Mono-protection of diol **976** gave alcohol **977** in quantitative yield by known conditions.⁹⁵ Swern oxidation of this substrate⁹⁶ efficiently afforded aldehyde **971** in 86% yield.

Scheme 4.57



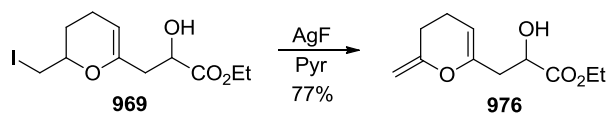
Aldehyde **974** was prepared from ester **978** in two steps (Scheme 4.58). Silyl protection of both hydroxyls provided silyl ether **977** in 83% yield. Partial reduction of the ester moiety upon treatment with di-*iso*-butylaluminum hydride⁹⁷ then provided aldehyde **974** in high yield.

Scheme 4.58



After carbonyl-ene reactions were successfully performed on the iodinated substrate **302**, elimination to the corresponding exocyclic enol ethers was effected. Two methods for the conversion of the iodomethyl group to an exocyclic enol ether were explored. The first focused on the reaction with silver fluoride in pyridine and provided enol ether **976** in 77% yield (Scheme 4.59). A second method was explored that would be compatible with silyl-protected substrates: DBU facilitated elimination. Not only did these reaction conditions work on silylated substrates (Table 4.5, entries 3 and 5), but also produced enol ether **976** (entry 1) in higher yield (93%). For these reasons, the DBU elimination was the preferred method of

Scheme 4.59



dehydrohalogenation. In all cases, the elimination of iodine proceeded smoothly to provide desired exocyclic enol ethers in good to excellent yields.

Table 4.5: DBU Elimination of Carbonyl-Ene Adducts

Entry	Iodide	Enol Ether	Yield
1			93%
2			92%
3			100%
4			80%
5			89%

Upon formation of the second exocyclic enol ether the stage was set to explore the final phase of the synthesis. The newly formed enol ethers were subjected to a second carbonyl-ene reaction to afford the bis- β -hydroxy pyrans (Tables 4.6-4.8). The carbonyl-ene reaction of these 2-methylenedihydropyrans with ethyl glyoxylate was first evaluated (Table 4.6). As before, ethyl glyoxylate proved to be an excellent substrate, and generally provided bis- β -hydroxypyranes in good to excellent yields as 1:1 mixtures of diastereomers. These reactions proceeded in the presence of 5% ZnCl_2 after a relatively short reaction time. The presence of glyoxylate polymer as a byproduct in these reactions made purification of the fairly polar product difficult by chromatography. Therefore two equivalents of the enol ether were used for each equivalent of

ethyl glyoxylate to avoid polymer formation. The excess enol ether was quantitatively recoverable in all cases, without any observed double bond isomerization.

Table 4.6: Ene Reactions of 2-Methylenedihydropyrans with Ethyl Glyoxylate

Entry	Enol Ether ^a	Product	Yield ^b
1			89%
2			80%
3			70%
4			92%
5			99%

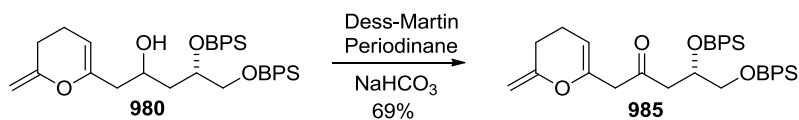
^a 2 equivalents

^b obtained as a 1:1 mixture of diastereomers

^c prepared by DMP oxidation of **287**

Enol ether **985** was prepared from enol ether **980** by oxidation with Dess-Martin Periodinane (Scheme 4.60). The purpose of this oxidation was to simplify the product mixture that would result from the second carbonyl-ene reaction. If enol ether **980** were used in the reaction, up to four diastereomers could result.

Scheme 4.60



Reactions of the same 2-methylenedihydropyrans with *p*-nitrobenzaldehyde, a relatively activated aldehyde, produced only low yields of the desired products when treated with 5 mol% ZnCl_2 over 48 hours (Table 4.7, entry 1). Rather, longer reaction times and equimolar amounts

Table 4.7: Ene Reactions of 2-Methylenedihydropyrans with *p*-Nitrobenzaldehyde

Entry	Enol Ether	Product	Mol % ZnCl_2	Yield ^a
1			5	15%
2			100	77%
3			100	54%
4			100	51%
5			100	53%

^acompounds isolated as a 1:1 mixture of diastereomers

^bReaction time 36 h, performed by T. Lam

of zinc chloride were required to obtain adequate product yields. It is not entirely unexpected that lower yields are associated with the carbonyl-ene reactions of less activated enophile components because the presence of the endocyclic double bond is expected to reduce reactivity.⁹⁸

Along these lines, the carbonyl-ene reaction of 2-methylenedihydropyrans with non-activated aldehydes did not provide any of the desired products (Table 4.8). Trials combining enol ether **978** and silyl ether aldehyde **971** with various amounts of ZnCl₂, ranging from 20 to 100 mol % (entries 1-3), resulted in consumption of the starting enol ether, without production of the desired pyrans. Likewise, ene reactions using benzaldehyde **479** as the enophile did not yield the desired dihydroxypyran (entry 4).

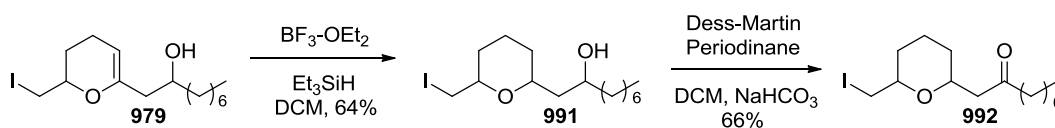
Table 4.8: Carbonyl-Ene reaction of Aliphatic Aldehydes with 2-Methylenedihydropyrans

Entry	Enol Ether	Aldehyde	Mol % ZnCl ₂	Yield (%)
1	 978	 971	20	0%
2	 978	 971	50	0%
3	 978	 971	100	0%
4	 979	 479	100	0%

As these results show, the carbonyl-ene reaction of 2-methylenedihydropyrans generally proceeds in moderate to high yields when activated aldehydes are used. This is not the case with non-activated aldehydes. These substrates give none of the anticipated ene adducts even in the presence of equimolar amounts of ZnCl_2 . The reactions of 2-methylenedihydropyrans are therefore limited by the type of enophile that can be coupled under these conditions. As noted above the internal double bond present in these enol ethers draws electron density away from the dihydropyran oxygen. Thus these types of enol ethers are not as reactive as their tetrahydropyranyl equivalents because the internal oxygen is less capable of donating electrons to the reactive, exocyclic olefin. In order to overcome the limitations of this reaction, two options were considered: use of a stronger Lewis acid to facilitate aldehyde activation or reduction of the endocyclic enol ether prior to elimination. Because exo enol ether substrates are such labile compounds, the later route was examined.

In an effort to prepare a more reactive substrate for the bi-directional carbonyl-ene reaction with non-activated enophiles, the synthesis of enol ether **995** was attempted (Scheme 4.61). By reducing the dihydropyran double bond, we hoped to avoid the charge delocalization

Scheme 4.61

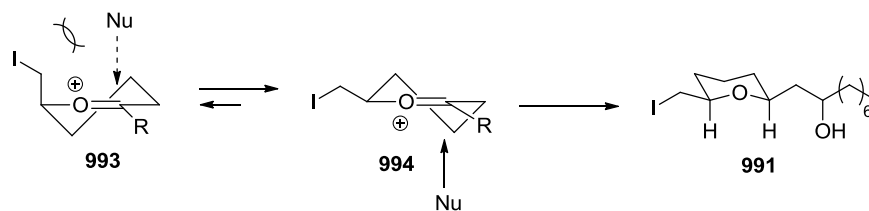


experienced by the ring oxygen in the 2-methylenedihydropyran intermediates, and thus make a more reactive enol ether. Thus, dihydropyran **979** was treated with triethylsilane in the presence of $\text{BF}_3\text{-OEt}_2$ to give the 2,6-disubstituted tetrahydropyran as a 1:1 mixture of diastereomers.

Oxidation of secondary alcohol **991** was then performed using Dess-Martin periodinane in order to simplify the product mixture. A single ketone diastereomer **992** was isolated.

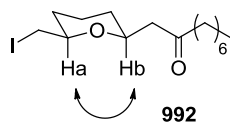
Reduction of dihydropyran **979** is expected to give the *cis*-2,6-tetrahydropyran on both stereoelectronic⁹⁹ and steric grounds. The oxonium ion intermediate formed in this reaction is expected to adopt a half-chair conformation. The two possible conformations of this intermediate are either oxonium ion **993** or **994**, the latter of which is lower in energy (Scheme 4.62). Axial attack of the nucleophile is favored on stereoelectronic grounds where the reaction

Scheme 4.62



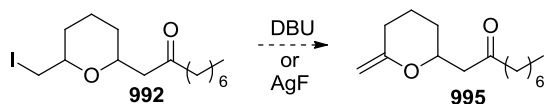
proceeds through a chair transition-state. In contrast, equatorial attack proceeds through a higher energy boat transition state and in the absence of competing steric effects, will be disfavored. Axial addition to intermediate **993** is disfavored due to steric interactions between the approaching nucleophile and the pseudoaxial iodomethyl group at C₆. Therefore, it is expected that the *cis* stereoisomer predominates based on axial attack of hydride on the low energy conformer **994**. The nOe studies on ketone **992** are consistent with this expectation. Irradiation of Ha led to the strong enhancement of the Hb resonance and likewise, irradiation of Hb caused enhancement of Ha (Figure 4.11).

Figure 4.11



With the desired tetrahydropyran ring in hand, dehydrohalogenation of iodide **992** was subsequently attempted in order to prepare the corresponding exocyclic enol ether **995** (Scheme 4.63). Upon treatment with DBU only recovered iodide **992** was obtained albeit in 23% yield. No other identifiable products were isolated, and TLC of the crude reaction mixture showed only the spot corresponding to the unreacted starting material. When silver fluoride was used to effect elimination, iodide **992** was completely consumed, but none of the desired enol ether **995** was isolated. ^1H NMR and TLC of the crude reaction mixture did not show the presence of any discernible compounds. In light of these difficulties, focus shifted to the synthesis of bis-spiroketal from bis- β -hydroxypyran.

Scheme 4.63



Progress Toward Trioxadispiroketal Synthesis

With the development of an effective route to bis- β -hydroxypyran the next stage was the application of this chemistry for the synthesis of trioxadispiroketal. The interest in synthesizing bis- β -hydroxypyran lies partially in the manufacture of bis-spiroketal units like those seen in the northern fragment of the spirastrellolides.

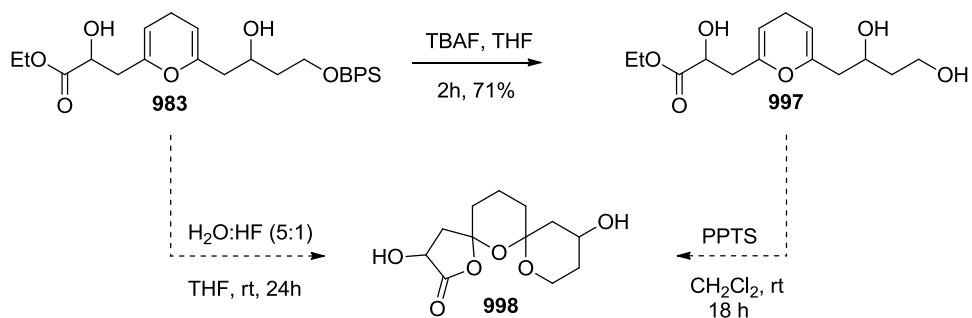
Work toward the synthesis of a (5,6,6)-trioxadispiroketal system akin to the northern fragment of the spirastrellolides, was attempted previously in the lab.⁹⁷ The spirocyclization of β -hydroxy- β -keto-pyran **986** proved difficult (Scheme 4.64). The two-step desilylation and cyclization of this pyran was attempted for the synthesis of (5, 6, 6)-trioxadispiroketal **996**. Subjection of pyran **986** to TBAF and subsequent treatment of the crude mixture with PPTS did not provide the desired spiroketal product nor was the starting pyran recovered.

Scheme 4.64



The inability to cyclize pyran **986** prompted the study of spirocyclization conditions that are conducive to these sensitive bis- β -oxygenated pyran substrates. Spirocyclization studies began with bis- β -hydroxypyran **983** (Scheme 4.65). In theory this pyran should spiroketalize into the same (5,6,6)-trioxadispiroketal ring system as bis-spiroketal **996**, but is made in fewer synthetic steps. Direct treatment with hydrofluoric acid should deprotect and concurrently cyclized the pyran to form trioxadispiroketal **998**. Under these conditions however, no discernable products were obtained, although all starting material was consumed. As both Paterson¹⁰⁰ and Forsyth¹⁰¹ had observed decomposition in the presence of strong acid in related systems, we sought milder acidic conditions. Therefore a second, two-step approach was explored for the synthesis of the bis-spiroketal **998**. Silyl deprotection with tetrabutylammonium fluoride yielded the triol **997** in good yield. This triol was carried on crude to the next reaction. Spiroketalization was then attempted under mildly acidic conditions.

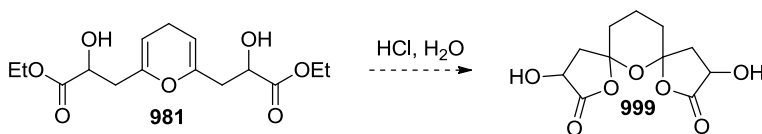
Scheme 4.65



Treatment of triol **997** with PPTS showed complete consumption of starting material after eighteen hours at room temperature. The reaction progress was carefully monitored by TLC throughout the experiment, though no distinct product spots emerged. ¹H NMR of the crude reaction mixture did not show the presence of any identifiable compounds.

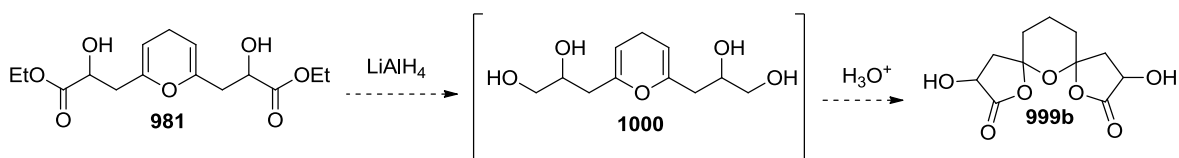
Earlier work in our lab demonstrated the feasibility of using an ester nucleophile directly for the preparation of spiroketals **964** and **965** using HCl (scheme 4.54). The direct, acid catalyzed cyclization of diester pyran **981** was thus attempted in an effort to prepare the (5,6,5) bis-spiroketal **999** (Scheme 4.66). Application of these same acidic conditions to pyran **981** did not have the same result. The TLC of the reaction showed disappearance of the pyran, with no other spot emerging, even with use of polar solvent systems. The ¹H NMR of the crude residue did not show any apparent products.

Scheme 4.66



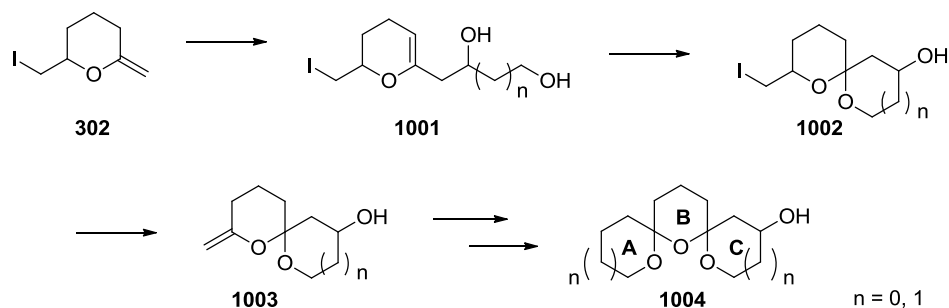
In a second approach to trioxadispiroketal **999**, the ester groups were reduced prior to cyclization (Scheme 4.67). Thus, diester **981** was treated with LiAlH_4 to give the presumed tetrahydroxy-intermediate **1000** that was not isolated, but subjected immediately to aqueous acidic workup. Again TLC of the reaction mixture showed disappearance of the starting material, without the emergence of any new spots, even with polar solvents. The tetrahydroxy intermediate, if formed, would be highly polar and would most likely be lost in the aqueous workup. The same could be true of any spiroketal systems formed if they proved to be polar enough, although TLC of the aqueous layers did not show the presence of any organic compounds.

Scheme 4.67



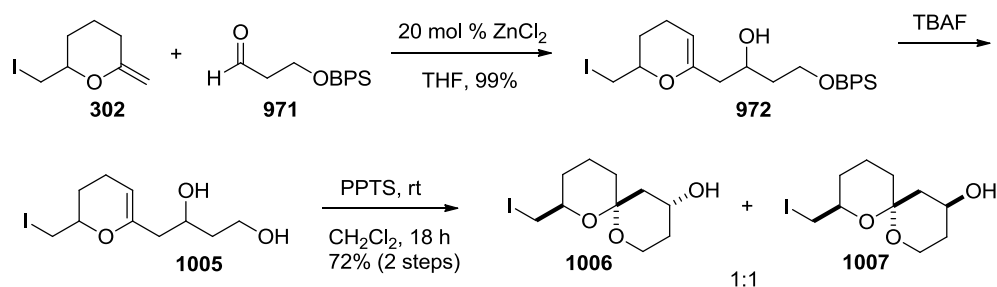
The failure to prepare the bis-spiroketal directly from the bis-β-hydroxypyran may be due to the inherent sensitivity of these systems. These concerns led us to explore an alternative, stepwise approach for trioxadispiroketal synthesis. It is anticipated that the original sequence for bis-β-hydroxy-dienol ethers **966** (Scheme 4.55) could be intercepted such that formation of the first spiroketal system (BC) (Scheme 4.68) precedes elimination to generate the new exocyclic enol ether. Potential advantage of this approach over direct cyclization is that bis-spiroketal derived from two non-activated aldehydes may now be available because reactivity of exo enol ether **1003** is not attenuated by the presence of an endo enol ether.

Scheme 4.68



Efforts focused on the synthesis of the (6,6,6)-bis-spiroketal **1004** ($n = 1$) (Scheme 4.69). The carbonyl-ene reaction of enol ether **302** with aldehyde **971** (Scheme 4.69) very efficiently provided ene adduct **972** in the presence of 20 mol% ZnCl_2 . Silyl deprotection afforded diol **1005**, which was carried on crude to the next reaction. Acid catalyzed cyclization with PPTS

Scheme 4.69



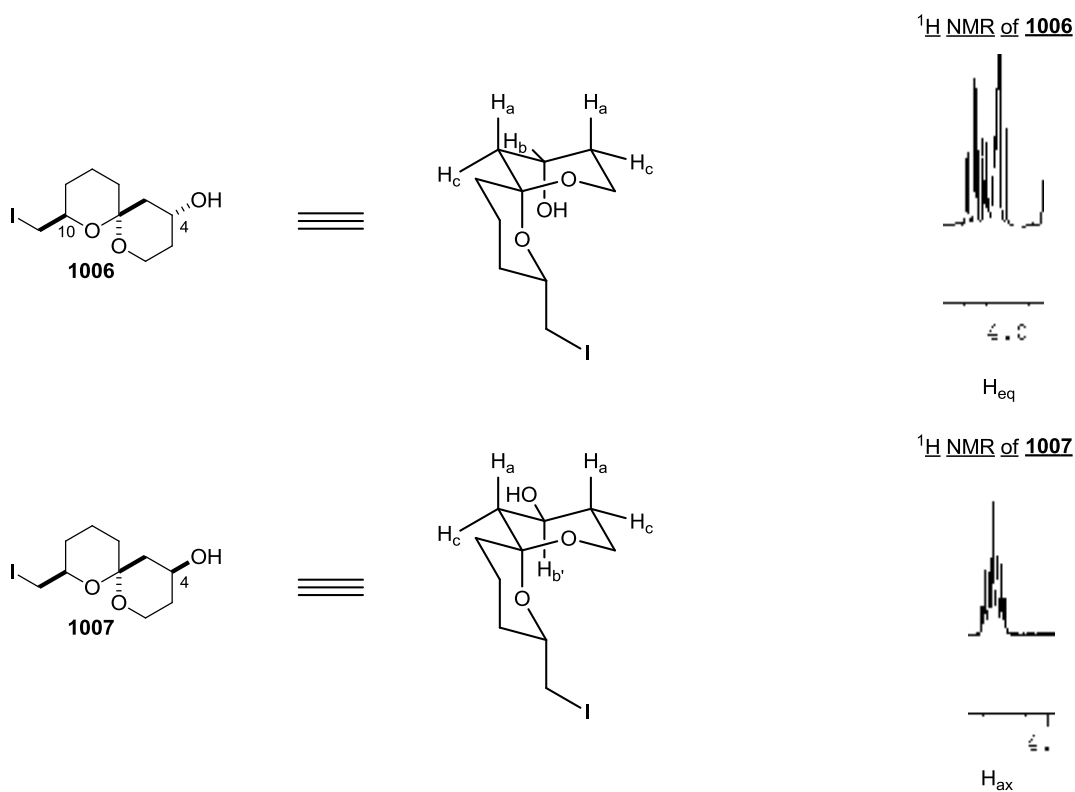
yielded spiroketals **1006** and **1007** as a 1:1 mixture of diastereomers. These diastereomers were separated by flash column chromatography and carried on individually as described below.

As the spiroketalization was conducted under thermodynamic conditions, formation of the most stable carbon framework was expected. This framework should contain an equatorial iodomethyl group and would benefit from double anomeric stabilization. For this reason the resulting diastereomers **1006** and **1007** were presumed to differ only in the stereochemistry of the

secondary alcohol. The identity of the individual isomers was confirmed on the basis of ^1H NMR coupling constants.

The stereochemistry for each isomer was determined by evaluating the coupling constants for the hydrogen at C_4 (H_b) (Figure 4.12). In each case the angles between the proton.

Figure 4.12



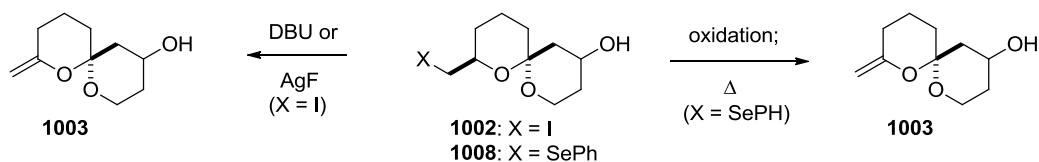
at this position and those at adjacent positions are assumed to be similar, thereby simplifying the resonance pattern. Compound **1006** possesses an axial alcohol, and therefore both J_{ba} and J_{bc} are expected to be small. Since the magnitude of these coupling constants should be similar, the H_4 resonance should appear as a narrow triplet in the ^1H NMR. An equatorial orientation of H_b is expected to exhibit small-small coupling patterns. Conversely, compound **1007**, which has an

equatorial alcohol, it is expected $J_{b'a}$ to be large and $J_{b'c}$ to be small. Therefore the C₄ proton peak in the ¹H NMR is expected to appear as a doublet of doublets.

Examination of the relevant portions of the ¹H NMRs show that the peaks are somewhat in agreement with these expectations. Spiroketal **1006** shows a narrow peak at 4.08 ppm. This peak overlaps slightly with a peak associated with C₁₀ at 4.14 ppm. This peak is not the narrow triplet expected, due to non-equivalent coupling constants associated with the adjacent protons. Nonetheless this peak is narrower than that associated with spiroketal **1007**. Likewise the peak representing H_{b'} in compound **1007** is not the expected doublet of doublets, but does represent the presence of a larger coupling constant.

With spiroketals **1006** and **1007** in hand, attention was turned to the formation of exocyclic enol ether **1003** (Scheme 4.70). Two methods were evaluated: the base-induced elimination of iodine under conditions previously established for the preparation of bis-enol pyrans **976-980** (*cf.* Table 4.5) and internal elimination of a selenoxide.

Scheme 4.70



Elimination was first attempted on iodide **1006**. Treatment with DBU proved unsuccessful and resulted only in 62% recovery of starting material (Table 4.9, entry 1). Elimination was also attempted with silver fluoride both at room temperature (entry 2) and 65°C (entry 3). At room temperature only the starting iodide was isolated in 86%. Since the reactivity

Table 4.9

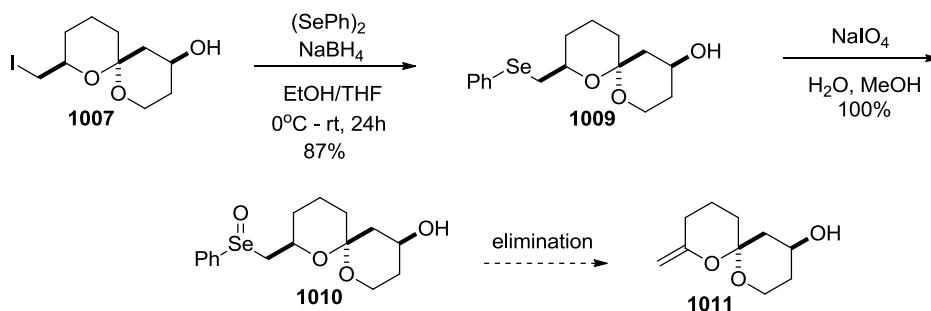


Entry	Condition	Temperature (°C)	Time (hr)	Yield	Sm Rec
1	DBU, PhH	65	24	0%	62%
2	AgF, pyr	25	24	0%	86%
3	AgF, pyr	65	24	0%	31%

was low, higher temperatures were applied to the same reaction, but only the starting iodide was isolated in 31% or the iodide was replaced by fluorine (26%). The difficulty observed in eliminating the iodide may be due to steric hindrance. The proximal stereocenter may block access of the base to the C₁₀ hydrogen, thereby impeding the formation of the double bond. The difficulties experienced with these reactions prompted an approach involving internal elimination.

In a second approach, iodide **1007** was converted to the selenoxide **1010** (Scheme 4.71). We anticipated that elimination of the selenoxide might work better for this system since the

Scheme 4.71



reaction is intramolecular. In practice, iodide **1006** was treated with diphenyl selenide and sodium borohydride to give the selenide **1009** in 87% yield.¹⁰² This compound was subsequently oxidized to selenoxide **1010**,¹⁰³ which upon workup, was directly subjected to elimination conditions without further purification. Several solvents were used to facilitate the elimination including tetrahydrofuran, dihydropyran, and dimethylsulfide (Table 4.10, entries 1-3).¹⁰⁴ None of the desired exocyclic enol ether **1011** was formed in either THF or DHP though a trace amount of this product **1011** was detected by ¹H NMR using dimethylsulfide as solvent. The small quantities of material produced precluded further pursuit of this sequence.

Table 4.10

Entry	Solvent	Temperature (°C)	Time (hr)	Yield
1	THF	65	5	0
2	DHP ^a	38	5	0
3	DMS	86	5	trace

^a3,4-dihydro-2H-pyran

4.4 Conclusions

We have demonstrated a facile approach to the preparation of bis-β-hydroxypyran through two-directional carbonyl-ene reactions of exocyclic enol ethers. The use of an iodomethyl derivative as the bis-exo enol ether equivalent facilitates this process and allows for the preparation of non-symmetrical systems. The initial ene reaction in the sequence proceeds cleanly in the presence of 5 mol% ZnCl₂. The intermediate 6-methylene-dihydropyran prepared

is more stable than expected, though participates in the carbonyl-ene reactions of activated enophiles in good to excellent yields in the presence of 20 mol% ZnCl_2 . The reaction of the bis-enol ether with unactivated aldehydes was more troublesome and was not observed even in the presence of equimolar amounts of ZnCl_2 . Use of stronger Lewis acids may overcome this difficulty and allow us to further broaden the substrate scope. Overall, this method represents an efficient method for the formation of bis- β -hydroxypyran, compounds that may prove useful for the preparation of tetrahydropyran-containing natural products.

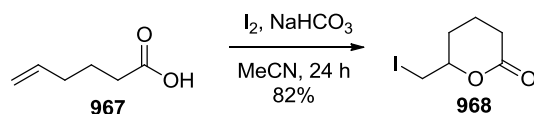
The current data suggests that the synthesis of trioxadispiroketal from bis- β -hydroxy precursors is non-trivial. The inability to produce these complex systems from these pyran precursors is most likely due to their sensitivity. Further examination of the reaction conditions will be required to effect trioxadispiroketal formation. This truly would be a unique method for bis-spiroketal construction. Advantages of this method include its highly convergent nature and potential ease with which a number of different spiroketals could be formed from a common intermediate. The formation of these bis-spiroketal is of high interest due to their presence in interesting, biologically active metabolites.

4.5 Experimentals

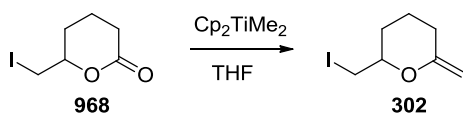
General Methods

All air sensitive reactions were performed in oven dried glassware under an atmosphere of argon. Reaction solvents were dried over CaH_2 (benzene, dichloromethane), or sodium/benzophenone ketyl (tetrahydrofuran, diethyl ether) and were distilled just prior to use. All other reagents were reagent grade and purified as necessary. Analytical thin layer chromatography was performed on EM silica gel 60 F254 glass plates (0.25 mm). Visualization of analytical thin layer chromatography was achieved using UV absorbance (254 nm) and ceric ammonium molybdate stain. Melting points were recorded using an Electrothermal melting point apparatus and are uncorrected. Flash column chromatography was performed using SiliaFlash P60 silica gel (40-60 Å) from SiliCycle, Inc. ^1H NMR spectra were recorded on a Bruker Avance DPX-300 (300 MHz) spectrometer. Chemical shifts are reported in ppm, downfield from tetramethylsilane using residual CHCl_3 as the internal standard (δ 7.27 ppm). ^{13}C NMR spectra were recorded on a Bruker Avance DPX-300 (75 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm, downfield from tetramethylsilane using residual CHCl_3 as the internal standard (δ 77.0 ppm). IR spectra were obtained with a Thermo Nicolet IR-100 spectrometer on NaCl plates. Elemental Analyses were performed by Complete Analysis Laboratories, Inc.; Parsippany, NJ. High resolution mass spectra were obtained using the positive ion electrospray mode on a Bruker 12 Tesla APEX-Qe FTICR-MS with an Apollo II ion source at Old Dominion University, Norfolk, VA.

Experimental Procedures

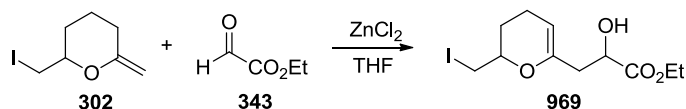


Lactone 968. To a solution of iodine (26.0g, 0.315 mol) and $NaHCO_3$ (16.0g, 62.9 mmol) in acetonitrile (175 mL) was added carboxylic acid **967** (4.00g, 31.5 mmol). The reaction was stirred at room temperature for 24 hours. The reaction mixture was then diluted with EtOAc (50 mL) and washed with a saturated sodium thiosulfate solution (40 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (3 x 40 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2 ; hexanes:EtOAc, 5:1-4:1) to afford tetrahydropyran **968** (6.55g, 82%) as a yellow oil. 1H NMR data for this compound agreed with the known literature values.¹⁰⁵ TLC: R_f = 0.23 (hexanes:EtOAc, 2:1). 1H NMR ($CDCl_3$, 300 MHz): δ 4.28 (1H, m), 3.33 (2H, m), 2.58 (1H, m), 2.45 (1H, m), 2.16 (1H, m), 1.91 (2H, m), 1.62 (1H, m).

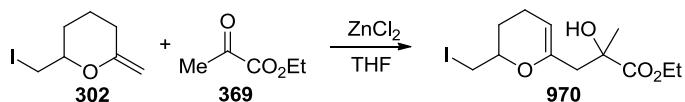


Enol ether 302. To a solution of lactone **968** (0.75g, 3.13 mmol) in THF (42 mL) was added dimethyl titanocene (12.5 mL of a 0.5M solution in THF, 6.26 mmol) in the dark. The reaction mixture was heated to reflux and stirred in the dark for 24 h. After cooling to room temperature, solvent was removed *in vacuo* to approximately half the volume. The residue was diluted with hexanes (500 mL) and filtered through Celite. The solvent was removed *in vacuo* and the resulting crude residue was purified by flash chromatography using deactivated silica gel (SiO_2 ;

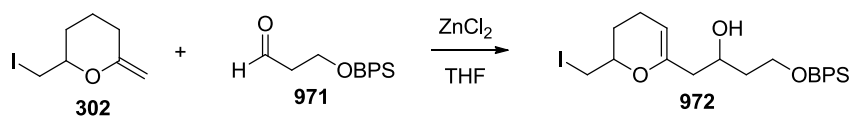
hexanes:Et₃N, 95%:5%) to afford enol ether **302** (0.56 mg, 76%) as a yellow liquid. TLC: R_f = 0.67 (hexanes:EtOAc, 10:1). ¹H NMR (CDCl₃, 300 MHz): δ 4.37 (1H, d, *J* = 1.2 Hz), 4.09 (1H, d, *J* = 1.5 Hz), 3.58 (1H, m), 3.24 (2H, dd, *J* = 5.7, 1.2 Hz), 2.15 (2H, m), 1.69 (4H, m). ¹³C NMR (CDCl₃, 75 MHz): δ 159.3 (C), 92.4 (CH₂), 77.6 (CH), 30.1 (CH₂), 28.5 (CH₂), 21.9 (CH₂), 9.1 (CH₂). IR (film): 2946, 2868, 1652, 1252 cm⁻¹. HRMS (ESI) Calcd for C₇H₁₁IO ([M+Na]⁺): 498.9601, found 498.9613.



Dihydropyran 969: Ethyl glyoxylate (0.12 mL, 1.19 mmol) was added to a solution of enol ether **302** (235 mg, 0.992 mmol) in dry THF (1.7 mL) followed by 0.30 mL of a freshly prepared solution of ZnCl₂ (22.4 mg/mL, 0.049 mmol) in dry THF. The reaction was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO₂; hexanes:EtOAc, 10:1) to afford dihydropyran **969** (281 mg, 84%) as a yellow oil with a diastereomeric ratio of 1:1. TLC: R_f = 0.34 (hexanes:EtOAc, 3:1). ¹H NMR (CDCl₃, 300 MHz): δ 4.61 (1H, q, *J* = 3.7 Hz), 4.35 (1H, m), 4.24 (2H, q, *J* = 7.1 Hz), 3.87 (0.5H, m), 3.77 (0.5H, m), 3.27 (2H, m), 3.09 (0.5H, br s), 2.98 (0.5H, br s), 2.50 (2H, m), 2.04 (3H, m), 1.67 (1H, m), 1.30 (1.5H, t, *J* = 7.1 Hz), 1.30 (1.5H, t, *J* = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 174.2 (C), 174.0 (C), 149.3 (C), 149.0 (C), 99.0 (2) (CH), 74.8 (CH), 74.0 (CH), 68.9 (CH), 68.6 (CH), 61.4 (CH₂), 38.9 (2) (CH₂), 27.0 (CH₂), 26.9 (CH₂), 19.7 (CH₂), 19.5 (CH₂), 14.3 (CH₃), 14.2 (CH₃), 8.4 (CH₂), 7.8 (CH₂). IR (film): 3494, 2926, 1735, 1681, cm⁻¹. HRMS (ESI) Calcd for C₁₁H₁₇IO₄ ([M+Na]⁺): 363.0064, found 363.0066.

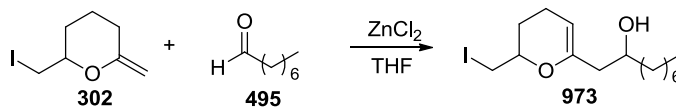


Dihydropyran 970: Ethyl pyruvate (77 mg, 0.67 mmol) was added to a solution of enol ether **302** (140 mg, 0.556 mmol) in dry THF (0.1 mL) followed by 1.0 mL of a freshly prepared solution of ZnCl_2 (15 mg/mL, 0.11 mmol) in dry THF. The reaction was stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2 ; hexanes:EtOAc, 10:1) to afford dihydropyran **970** (142 mg, 66%) as a yellow oil with a diastereomeric ratio of 1:1. TLC: $R_f = 0.65$ (hexanes:EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 4.59 (1H, m), 4.22 (2H, m), 3.87 (0.5H, m), 3.75 (0.5H, br s), 3.68 (0.5H, m), 3.51 (0.5H, br s), 3.25 (2H, m), 2.57 (1H, m), 2.37 (1H, m), 2.01 (3H, m), 1.64 (1H, m), 1.44 (3H, d, $J = 3.1$ Hz), 1.31 (3H, m). ^{13}C NMR (CDCl_3 , 75 MHz): δ 175.8 (C), 175.5 (C), 149.9 (C), 149.5 (C), 99.5 (CH), 99.4 (CH), 75.1 (CH), 74.4 (CH), 73.9 (CH), 73.8 (CH), 61.4 (2) (CH_2), 44.9 (2) (CH_2), 27.0 (2) (CH_2), 25.7 (CH_3), 25.6 (CH_3), 19.9 (CH_2), 19.6 (CH_2), 14.3 (2) (CH_3), 8.7 (CH_2), 7.6 (CH_2). IR (film): 3526, 3066, 2980, 1731, 1679 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_{19}\text{IO}_4$ ($[\text{M}+\text{Na}]^+$): 377.0220, found 377.0224.

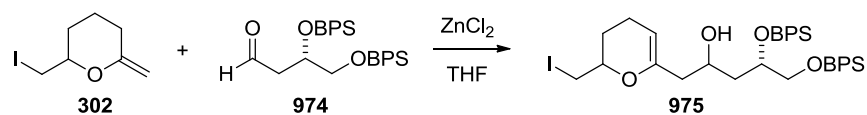


Dihydropyran 972: Aldehyde **971** (296 mg, 0.95 mmol) was added to a flask containing enol ether **1** (188 mg, 0.79 mmol) followed by 1.58 mL of a freshly prepared solution of ZnCl_2 (13 mg/mL, mmol) in dry THF. The reaction was stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2 ; hexanes:EtOAc, 20:1) to afford dihydropyran **972** (428 mg, 99%) as a yellow oil with a diastereomeric ratio of 1:1. TLC: $R_f = 0.75$ (hexanes:EtOAc, 3:1). ^1H NMR (CDCl_3 , 300 MHz):

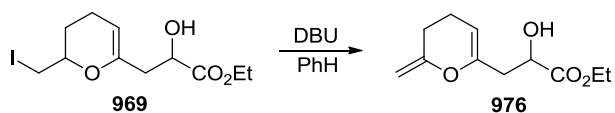
δ 7.72 (4H, m), 7.42 (6H, m), 4.58 (1H, t, $J = 3.6$ Hz), 4.13 (1H, m), 3.88 (2H, q, $J = 5.8$ Hz), 3.86 (2H, m), 3.28 (2H, dd, $J = 5.8, 2.5$ Hz), 3.18 (1H, s), 2.25 (2H, d, $J = 6.1$ Hz), 2.03 (2H, m), 1.75 (2H, q, $J = 5.9$ Hz), 1.67 (2H, m), 1.07 (9H, s). ^{13}C NMR (CDCl_3 , 75 MHz): δ 151.3 (C), 135.5 (CH), 134.8 (CH), 133.4 (C), 133.3 (C), 129.7 (CH), 129.6 (CH), 127.7 (CH), 97.7 (C), 97.6 (C), 74.4 (CH), 74.3 (CH), 68.8 (CH), 62.6 (CH_2), 62.5 (CH_2), 41.9 (CH_2), 38.4 (2) (CH_2), 27.2 (CH_2), 27.1 (CH_2), 26.8 (CH_3), 26.5 (CH_3), 19.7 (CH_2), 19.1 (C), 8.5 (CH_2), 8.4 (CH_2). IR (film): 3433, 3069, 3047, 2929, 2855, 1676 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{35}\text{IO}_3\text{Si}$ ($[\text{M}+\text{Na}]^+$): 573.1292, found 573.1282.



Dihydropyran 973: Octyl aldehyde (340 mg, 2.66 mmol) was added to a solution of enol ether **302** (562 mg, 2.21 mmol) in dry THF (1.7 mL) followed by 2.7 mL of a freshly prepared solution of ZnCl_2 (22.4 mg/mL, 0.44 mmol) in dry THF. The reaction was stirred at room temperature for 11 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2 ; hexanes:EtOAc, 20:1) to afford dihydropyran **973** (695 mg, 82%) as a yellow oil with a diastereomeric ratio of 1:1. TLC: $R_f = 0.71$ (hexanes:EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 4.57 (1H, m), 3.84 (2H, m), 3.30 (2H, m), 2.47 (1H, dd, $J = 27.9, 3.6$ Hz), 2.27 (1H, m), 2.04 (4H, m), 1.66 (2H, m), 1.37 (10H, m), 0.88 (3H, t, $J = 6.7$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 151.7 (C), 97.9 (CH), 97.7 (CH), 74.5 (CH), 70.2 (CH), 70.1 (CH), 41.7 (CH_2), 36.8 (2) (CH_2), 31.8 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 27.3 (CH_2), 27.2 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 22.6 (CH_2), 19.8 (CH_2), 19.7 (CH_2), 14.1 (CH_3), 8.5 (CH_2), 8.4 (CH_2). IR (film): 3500, 3063, 2927, 2853, 1679 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{27}\text{IO}_2$ ($[\text{M}+\text{Na}]^+$): 389.0948, found 389.0954.

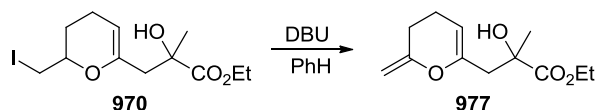


Dihydropyran 975: Aldehyde **974** (93.1 mg, 0.160 mmol) was added to a solution of enol ether **302** (45.6 mg, 0.192 mmol) in dry THF (0.13 mL) followed by 0.19 mL of a freshly prepared solution of ZnCl_2 (22.4 mg/mL, 0.032 mmol) in dry THF. The reaction was stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2 ; hexanes, 100%) to afford dihydropyran **975** (100.3 mg, 76%) as a yellow oil with a diastereomeric ratio of 2.7:2.7:1:1. TLC: R_f = 0.54 (hexanes:EtOAc, 5:1). ^1H NMR (CDCl_3 , 300 MHz): δ 7.45 (20H, m), 4.50 (0.24H, m), 4.44 (0.76H, m), 4.05 (2H, m), 3.74 (1H, m), 3.59 (2H, m), 3.21 (2H, dd, J = 5.6, 2.5 Hz), 2.86 (0.24H, dd, J = 6.6, 3.2 Hz), 2.70 (0.74H, dd, J = 6.0, 3.9 Hz), 1.86 (8H, m), 1.03 (6.6H, s), 1.02 (2.4H, s), 0.99 (6.6H, s), 0.98 (2.4H, s). ^{13}C NMR (CDCl_3 , 75 MHz): δ 151.2 (3) (C), 135.9 (CH), 135.7 (CH), 135.5 (3) (CH), 134.0 (C), 133.8 (C), 133.5 (C), 133.3 (C), 129.6 (CH), 129.5 (CH), 129.4 (CH), 127.5 (2) (CH), 127.4 (2) (CH), 97.7 (CH), 97.6 (CH), 77.2 (CH), 74.2 (2) (CH), 72.3 (CH), 67.1 (CH_2), 66.9 (CH), 41.8 (CH_2), 41.7 (CH_2), 40.8 (CH_2), 27.0 (CH_3), 26.8 (CH_3), 19.6 (CH_2), 19.5 (CH_2), 19.2 (CH_2), 19.1 (CH_2), 8.4 (CH_2), 8.3 (CH_2). IR (film): 3369, 3071, 2965, 2861, 1679, 1112 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{43}\text{H}_{55}\text{IO}_4\text{Si}_2$ ($[\text{M}+\text{Na}]^+$): 841.2576, found 841.2565.

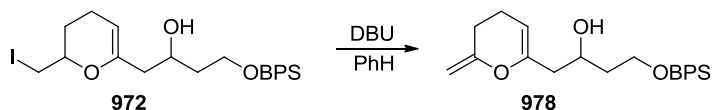


Dihydropyran 976: DBU (0.382 mL, 2.56 mmol) was added to a solution of iodide **969** (87 mg, 0.256 mmol) in benzene (4.7 mL). The reaction was heated to 65°C for a period of 24 h. Thereafter the reaction was cooled to room temperature, diluted with diethyl ether (50 mL) and filtered through celite. Column chromatography (SiO_2 ; hexanes:EtOAc, 10:1) yielded enol ether

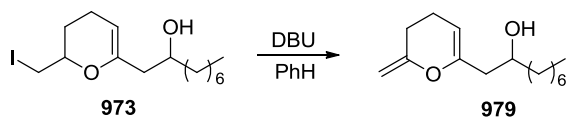
976 (50 mg, 93%) as a colorless oil. TLC: R_f = 0.42 (hexanes:EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 4.77 (1H, t, J = 4.0 Hz), 4.39 (1H, s), 4.35 (1H, m), 4.24 (2H, q, J = 7.1 Hz), 4.05 (1H, d, J = 0.8 Hz), 2.92 (1H, d, J = 6.7 Hz), 2.52 (2H, dq, J = 14.5, 4.6 Hz), 2.36 (2H, t, J = 6.6 Hz), 2.09 (2H, q, J = 6.5 Hz), 1.30 (3H, dt, J = 7.1, 0.4 Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 174.2 (C), 156.0 (C), 147.6 (C), 99.8 (CH), 89.9 (CH_2), 68.2 (CH), 61.5 (CH_2), 38.6 (CH_2), 25.6 (CH_2), 20.3 (CH_2), 14.1 (CH_3). IR (film): 3489, 2980, 2931, 1732, 1691, 1652 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{11}\text{H}_{16}\text{O}_4$ ($[\text{M}+\text{Na}]^+$): 235.0938, found 235.0938.



Dihydropyran 977: DBU (0.55 mL, 3.66 mmol) was added to a solution of iodide **970** (142 mg, 0.366 mmol) in benzene (7 mL). The reaction was heated to 65°C for a period of 24 h. Thereafter the reaction was cooled to room temperature, diluted with diethyl ether (50 mL) and filtered through celite. Column chromatography (SiO_2 ; hexanes:EtOAc, 10:1) yielded enol ether **977** (87 mg, 92%) as a colorless oil. TLC: R_f = 0.64 (hexanes:EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 4.73 (1H, t, J = 4.2 Hz), 4.33 (1H, s), 4.19 (2H, q, J = 7.1 Hz), 4.02 (1H, d, J = 0.8 Hz), 3.38 (1H, s), 2.60 (1H, d, J = 13.9 Hz), 2.33 (3H, m), 2.06 (2H, m), 1.42 (3H, s), 1.28 (3H, t, J = 7.2 Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 175.8 (C), 155.9 (C), 148.1 (C), 100.3 (CH), 89.9 (CH_2), 73.3 (C), 61.5 (CH_2), 44.6 (CH_2), 25.6 (CH_3), 25.5 (CH_2), 20.3 (CH_2), 14.1 (CH_3). IR (film): 3529, 3118, 3067, 2982, 1732, 1686, 1654 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_{18}\text{O}_4$ ($[\text{M}+\text{Na}]^+$): 249.1097, found 249.1095.

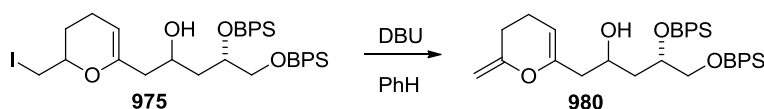


Dihydropyran 978: DBU (0.17 mL, 1.12 mmol) was added to a solution of iodide **972** (112 mg, 0.112 mmol) in benzene (2 mL). The reaction was heated to 65°C for a period of 24 h. Thereafter the reaction was cooled to room temperature, diluted with diethyl ether (50 mL) and filtered through celite. Column chromatography (SiO₂; hexanes:EtOAc, 20:1) yielded enol ether **978** (48 mg, 100%) as a colorless oil. TLC: R_f = 0.81 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 7.70 (4H, m), 7.43 (6H, m), 4.75 (1H, t, J = 4.1 Hz), 4.34 (1H, s), 4.16 (1H, m), 4.07 (1H, s), 3.88 (2H, m), 3.12 (1H, br s), 2.39 (2H, t, J = 6.6 Hz), 2.29 (2H, m), 2.12 (2H, m), 1.76 (4H, m), 1.08 (9H, s). ¹³C NMR (CDCl₃, 75 MHz): δ 156.4 (C), 149.9 (C), 135.5 (CH), 133.3 (C), 129.7 (CH), 127.7 (CH), 98.6 (CH), 89.8 (CH₂), 68.7 (CH), 62.8 (CH₂), 41.6 (CH₂), 38.2 (CH₂), 26.8 (CH₃), 25.8 (CH₂), 20.4 (CH₂), 19.1 (C). IR (film): 3500, 3071, 3050, 2931, 2857, 1687, 1652 cm⁻¹. HRMS (ESI) Calcd for C₂₆H₃₄O₃Si ([M+Na]⁺): 445.2170, found 445.2169.

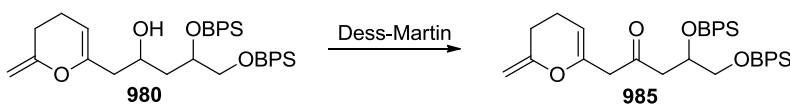


Dihydropyran 979: DBU (0.44 mL, 2.96 mmol) was added to a solution of iodide **973** (113 mg, 0.296 mmol) in benzene (5.5 mL). The reaction was heated to 65°C for a period of 24 h. Thereafter the reaction was cooled to room temperature, diluted with diethyl ether (50 mL) and filtered through celite. Column chromatography (SiO₂; hexanes:EtOAc, 20:1) yielded enol ether **979** (75 mg, 80%) as a colorless oil. TLC: R_f = 0.73 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 4.74 (1H, t, J = 4.2 Hz), 4.44 (1H, s), 4.09 (1H, d, J = 0.9 Hz), 3.82 (1H, m), 2.39 (2H, t, J = 6.6 Hz), 2.30 (1H, m), 2.12 (3H, m), 1.43 (2H, m), 1.29 (10H, s), 0.89 (3H, t, J = 6.8 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 156.2 (C), 150.1 (C), 98.8 (CH), 90.0 (CH₂), 69.3 (CH), 41.5 (CH₂), 36.7 (CH₂), 31.8 (CH₂), 29.6 (CH₂), 29.2 (CH₂), 25.7 (CH₂), 25.6 (CH₂), 22.6 (CH₂),

20.3 (CH₂), 14.1 (CH₃). IR (film): 3449, 3116, 2955, 2854, 1686, 1654 cm⁻¹. HRMS (ESI) Calcd for C₁₅H₂₆O₂ ([M+Na]⁺): 261.1825, found 261.1825.

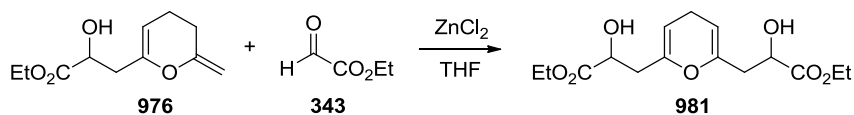


Dihydropyran 980: DBU (0.24 mL, 1.59 mmol) was added to a solution of iodide **975** (130 mg, 0.159 mmol) in benzene (3.5 mL). The reaction was heated to 65°C for a period of 24 h. Thereafter the reaction was cooled to room temperature, diluted with diethyl ether (20 mL) and filtered through celite. Column chromatography (SiO₂; hexanes:EtOAc, 50:1) yielded enol ether **980** (97 mg, 89%) as a yellow oil. TLC: R_f = 0.58 (hexanes:EtOAc, 5:1). ¹H NMR (CDCl₃, 300 MHz): δ 7.46 (20H, m), 4.64 (1H, m), 4.38 (1H, s), 4.04 (1H, s), 4.02 (2H, m), 3.56 (2H, m), 2.77 (0.14H, d, *J* = 2.8 Hz), 2.57 (0.86H, d, *J* = 3.5 Hz), 2.33 (2H, t, *J* = 6.7 Hz), 2.12 (4H, m), 1.79 (2H, m), 1.02 (7.7H, s), 1.01 (1.3H, s), 0.98 (7.7H, s), 0.96 (1.3H, s). ¹³C NMR (CDCl₃, 75 MHz): δ 156.2, 149.8, 135.9, 135.8, 135.7 (2), 135.5 (2), 135.4 (2), 133.9, 133.6, 133.3 (2), 133.2 (2), 129.7, 129.6, 129.5, 127.6, 127.5 (3), 127.4 (2), 98.6, 98.3, 89.9, 89.7, 77.4, 72.3, 72.0, 67.2, 66.7, 65.8, 42.1, 41.7, 40.8, 40.1, 26.9, 26.8, 25.8, 25.7, 20.3, 19.2, 19.1 (3). IR (film): 3570, 3071, 2930, 2857, 1686, 1651, 1112 cm⁻¹. HRMS (ESI) Calcd for C₄₃H₅₄O₄Si₂ ([M+Na]⁺): 713.3453, found 713.3437.

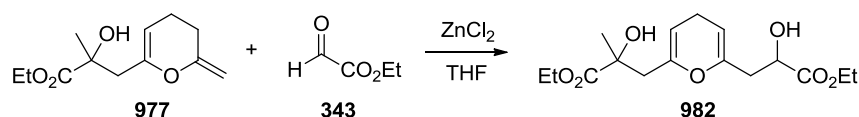


Ketone 985: To a solution of alcohol **980** (10.5 mg, 0.015 mmol) in CH₂Cl₂ (1.0 mL) was added Dess-Martin periodinane (7.4 mg, 0.017 mmol) at room temperature. The reaction stirred for 30 min and was then diluted with diethyl ether (5 mL), filtered through a pad of celite, and concentrated *in vacuo*. The crude residue was purified by flash chromatography using

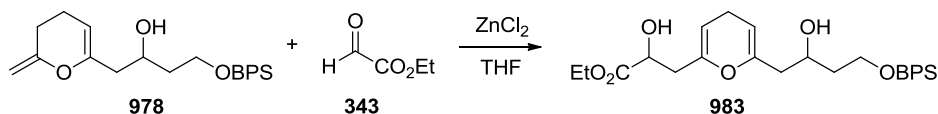
deactivated silica gel (SiO₂; hexanes:EtOAc, 100:1) to afford dihydropyran **985** (7.2 mg, 69%) as a yellow oil. TLC: R_f = 0.66 (hexanes:EtOAc, 5:1). ¹H NMR (CDCl₃, 300 MHz): δ 7.47 (20H, m), 4.65 (1H, t, J = 4.2 Hz), 4.38 (1H, s), 4.33 (2H, m), 4.04 (1H, s), 3.57 (2H, m), 2.93 (2H, s), 2.80 (2H, m), 2.33 (2H, t, J = 6.5 Hz), 2.07 (2H, q, J = 6.1 Hz), 1.00 (9H, s), 0.99 (9H, s). ¹³C NMR (CDCl₃, 75 MHz): δ 205.1, 155.9, 146.5, 135.9, 135.7, 135.5 (2), 133.9, 133.6, 133.3 (2), 129.6, 129.5 (2), 129.4, 127.5 (2), 127.4, 100.3, 90.3, 70.0, 67.0, 48.6, 45.9, 26.9, 26.8, 25.4, 20.4, 19.2 (2). IR (film): 3072, 2932, 2858, 1721, 1682 cm⁻¹. HRMS (ESI) Calcd for C₄₃H₅₂O₄Si₂ ([M+Na]⁺): 711.3296, found 711.3290.



Pyran 981: Ethyl glyoxylate (40 mg, 0.188 mmol) was added to a solution of enol ether **976** (40 mg, 0.188 mmol) in dry THF (0.05 mL) followed by 0.13 mL of a freshly prepared solution of ZnCl₂ (15 mg/mL, 0.018 mmol) in dry THF. The reaction was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO₂; hexanes:EtOAc, 3:1-1:1) to afford pyran **981** (25 mg, 89%) as a yellow oil. TLC: R_f = 0.11 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 4.61 (2H, m), 4.30 (6H, m), 3.63 (2H, br s), 2.69 (2H, s), 2.46 (4H, m), 1.32 (6H, m). ¹³C NMR (CDCl₃, 75 MHz): δ 174.1 (C), 174.0 (C), 146.9 (C), 146.0 (C), 98.9 (2) (CH), 68.6 (CH), 68.5 (CH), 61.6 (2) (CH₂), 38.5 (CH₂), 38.3 (CH₂), 21.0 (CH₂), 20.9 (CH₂), 14.2 (2) (CH₃). IR (film): 3464, 3067, 2983, 1739, 1674 cm⁻¹. HRMS (ESI) Calcd for C₁₅H₂₂O₇ ([M+Na]⁺): 377.1258, found 377.1266.

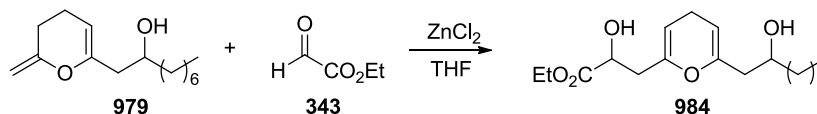


Pyran 982: Ethyl glyoxylate (0.0071 mL, 70 mmol) was added to a solution of enol ether **977** (0.020 mg, 77 mmol) in dry THF (0.10 mL) followed by 0.054 mL of a freshly prepared solution of ZnCl₂ (20 mg/mL, 0.003 mmol) in dry THF. The reaction was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO₂; hexanes:EtOAc, 3:1-1:1) to afford pyran **982** (20 mg, 80 %) as a yellow oil. TLC: R_f = 0.25 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 4.59 (2H, m), 4.27 (1H, m), 4.25 (2H, q, *J* = 7.1 Hz), 3.68 (1H, br d, *J* = 26.6 Hz), 2.68 (2H, s), 2.33 (2H, m), 1.44 (3H, d, *J* = 2.4 Hz), 1.30 (6H, tt, *J* = 7.1, 0.8 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 175.9 (C), 173.9 (C), 147.2 (C), 147.1 (3 (C), 99.5 (CH), 99.3 (CH), 98.6 (CH), 77.2 (C), 74.0 (CH₂), 73.7 (CH₂), 68.9 (CH), 68.8 (CH), 61.6 (CH₂), 44.2 (CH₂), 44.1 (CH₂), 38.5 (CH₂), 38.3 (CH₂), 29.7 (CH), 25.9 (CH₃), 25.7 (CH₃), 21.0 (CH₂), 20.9 (CH₂), 14.2 (CH₃). IR (film): 3258, 2982, 2851, 1734, 1672 cm⁻¹. HRMS (ESI) Calcd for C₁₆H₂₄O₇ ([M+Na]⁺): 351.1414, found 351.1417.

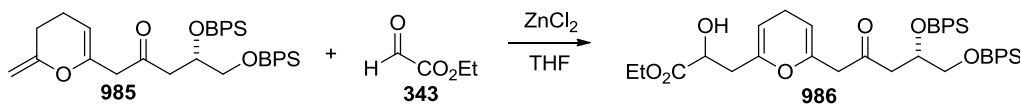


Pyran 983: Ethyl glyoxylate (68 mg, 0.665 mmol) was added to a solution of enol ether **978** (200 mg, 0.732 mmol) in dry THF (1.0 mL) followed by 0.50 mL of a freshly prepared solution of ZnCl₂ (10 mg/mL, 0.033 mmol) in dry THF. The reaction was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO₂; hexanes:EtOAc, 3:1-1:1) to afford pyran **983** (230 mg, 70%) as a yellow oil. TLC: R_f = 0.30 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 7.69 (4H, m), 7.42 (6H, m), 4.62 (1H, m), 4.58 (1H, m), 4.33 (1H, m), 4.24 (2H, m), 4.10 (1H, m), 3.86 (2H, m), 3.31 (1H, br s), 3.06 (1H, br s), 2.70 (2H, s), 2.55 (1H, dd, *J* = 14.5, 4.5 Hz), 2.41 (1H, dd, *J* = 14.5, 6.9 Hz), 2.20 (2H, d, *J* = 6.4 Hz), 1.74 (2H, q, *J* = 5.8 Hz), 1.29 (3H, dt, *J* = 7.1, 2.6), 1.06 (9H, s). ¹³C

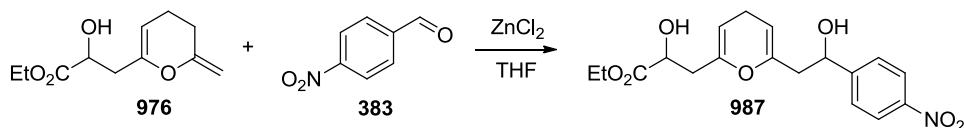
NMR (CDCl₃, 75 MHz): δ 174.1 (C), 148.8 (C), 148.6 (C), 146.8 (C), 135.5 (CH), 133.2 (C), 133.1 (C), 129.7 (CH), 127.7 (CH), 98.9 (2) (CH), 97.9 (CH), 97.7 (CH), 68.8 (CH), 68.5 (CH), 68.4 (CH), 68.3 (CH), 62.7 (CH₂), 61.6 (CH₂), 41.4 (CH₂), 38.5 (CH₂), 38.2 (2) (CH₂), 26.8 (CH₃), 21.0 (CH₂), 19.1 (C), 14.2 (CH₃). IR (film): 3483, 3071, 2931, 2857, 1736, 1672 cm⁻¹. HRMS (ESI) Calcd for C₃₀H₄₀O₆Si ([M+Na]⁺): 547.2486, found 547.2484.



Pyran 984: Ethyl glyoxylate (7 mg, 0.067 mmol) was added to a solution of enol ether **979** (34 mg, 0.134 mmol) in dry THF (0.11 mL) followed by 0.018 mL of a freshly prepared solution of ZnCl₂ (23 mg/mL, 0.003 mmol) in dry THF. The reaction was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO₂; hexanes:EtOAc, 3:1-1:1) to afford pyran **984** (22 mg, 92%) as a yellow oil. TLC: R_f = 0.36 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 4.63 (1H, m), 4.58 (1H, m), 4.34 (1H, dd, J = 6.9, 4.4 Hz), 4.25 (2H, m), 3.78 (1H, m), 2.70 (2H, s), 2.49 (2H, m), 2.21 (1H, m), 2.03 (1H, m), 1.44 (2H, m), 1.27 (10H, m), 0.88 (3H, t, J = 6.8 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 174.2 (C), 149.0 (C), 148.8 (C), 146.9 (C), 146.8 (C), 99.0 (CH), 98.0 (CH), 97.8 (CH), 69.5 (CH), 69.3 (CH), 68.5 (CH), 68.4 (CH), 61.7 (CH), 45.1 (CH₂), 41.3 (CH₂), 38.3 (2) (CH₂), 36.9 (CH₂), 36.8 (CH₂), 31.8 (CH₂), 29.6 (CH₂), 29.2 (CH₂), 25.7 (CH₂), 22.6 (CH₂), 21.0 (CH₂), 14.2 (CH₃), 14.1 (CH₃), 8.8 (CH₃). IR (film): 3499, 2928, 2856, 1737, 1673 cm⁻¹. HRMS (ESI) Calcd for C₁₉H₃₂O₅ ([M+Na]⁺): 363.2142, found 363.2142.

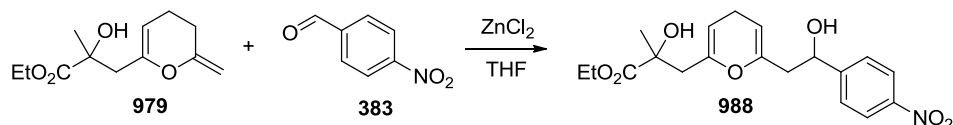


Pyran 986: Ethyl glyoxylate (8 μ L, 0.78 mmol) was added to a solution of enol ether **343** (7.0 mg, 0.010 mmol) in dry THF (50 μ L) followed by 20 μ L of a freshly prepared solution of ZnCl_2 (13.8 mg/mL, 0.002 mmol) in dry THF. The reaction was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2 ; hexanes:EtOAc, 3:1-1:1) to afford pyran **986** (8.0 mg, 99 %) as a yellow oil. TLC: R_f = 0.23 (hexanes:EtOAc, 5:1). ^1H NMR (CDCl_3 , 300 MHz): δ 7.48 (20H, m), 5.02 (1H, t, J = 4.2 Hz), 4.63 (1H, m), 4.49 (1H, m), 4.33 (1H, m), 4.24 (2H, m), 4.19 (2H, m), 3.57 (2H, m), 2.69 (5H, m), 2.88 (2H, s), 1.25 (3H, t, J = 7.1 Hz), 1.02 (9H, s), 1.02 (9H, s). ^{13}C NMR (CDCl_3 , 75 MHz): δ 205.0, 198.1, 174.1, 174.0, 146.8 (2), 145.2 (2), 135.9, 136.8, 135.7, 135.6, 135.5 (3), 134.0, 133.9, 133.6 (2), 133.4 (2), 133.3 (3), 129.6, 129.5 (3), 127.6, 127.5 (3), 127.4, 99.7, 98.7, 71.0 (2), 70.2 (2), 67.9 (2), 67.1 (2), 49.4, 48.3, 46.1 (2), 45.9, 38.4, 38.3, 26.9, 26.8, 22.3, 22.2, 21.4, 21.0, 19.2 (3), 17.5, 14.2, 14.1. IR (film): 3514, 3072, 2932, 2858, 1732, 1603, 1112 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{47}\text{H}_{58}\text{O}_7\text{Si}_2$ ($[\text{M}+\text{Na}]^+$): 813.3613, found 813.3617.

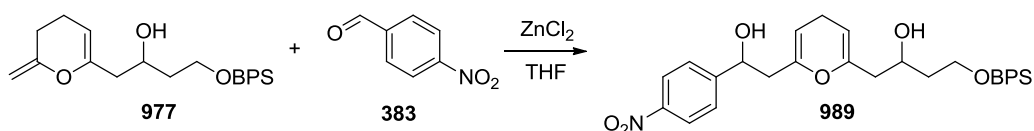


Pyran 987: *p*-Nitrobenzaldehyde (20.6 mg, 0.136 mmol) was added to enol ether **976** (24.0 mg, 0.114 mmol). 0.23 mL of a freshly prepared solution of ZnCl_2 (67.8 mg/mL, 0.114 mmol) in dry THF was added to the reaction flask. The reaction was stirred at room temperature for 48 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2 ; hexanes:EtOAc, 3:1-1:1) to afford pyran **987** (31.6 mg, 77%) as a yellow oil. TLC: R_f = 0.33 (hexanes:EtOAc, 1:1). ^1H NMR (CDCl_3 , 300 MHz): δ 8.19 (2H, d, J = 9.2 Hz), 7.55 (2H, d, J = 9.2 Hz), 5.04 (1H, m), 4.63 (1H, m), 4.56 (1H, m), 4.33 (1H, m), 4.26 (2H, q, J = 7.4 Hz), 2.67 (2H, m), 2.42 (6H, m), 1.30 (3H, t, J = 7.0 Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 151.2 (C), 148.6

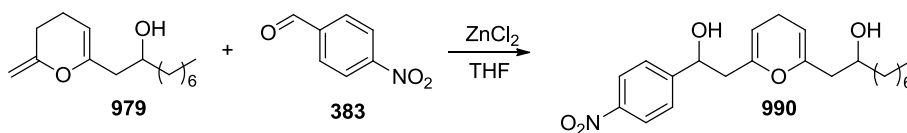
(C), 147.6 (C), 147.1 (C), 135.5 (CH), 132.9 (C), 129.8 (CH), 127.8 (CH), 126.4 (2) (CH), 123.5 (CH), 99.2 (CH), 99.1 (CH), 98.0 (CH), 97.9 (CH), 70.9 (CH), 70.7 (CH), 69.4 (CH), 69.2 (CH), 63.0 (CH₂), 45.1 (CH₂), 43.7 (CH₂), 43.6 (CH₂), 41.3 (CH₂), 38.0 (CH₂), 26.8 (CH₃), 20.9 (CH₂), 19.0 (C). IR (film): 3396, 3072, 2931, 2858, 1717, 1603, 1522, 1346 cm⁻¹. HRMS (ESI) Calcd for C₁₈H₂₁NO₇ ([M+Na]⁺): 386.1210, found 386.1211.



Pyran 988: *p*-Nitrobenzaldehyde (23 mg, 0.152 mmol) was added to a solution of enol ether **977** (33 mg, 0.127 mmol) in dry THF (0.08 mL) followed by 0.17 mL of a freshly prepared solution of ZnCl₂ (100 mg/mL, 0.127 mmol) in dry THF. The reaction was stirred at room temperature for 48 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO₂; hexanes:EtOAc, 3:1-1:1) to afford pyran **988** (28 mg, 54%) as a yellow oil. TLC: R_f = 0.20 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 8.21 (2H, d, *J* = 8.6 Hz), 7.57 (2H, dd, *J* = 8.8, 1.7 Hz), 5.01 (1H, m), 4.62 (1H, m), 4.56 (0.5H, m), 4.53 (0.5H, m), 4.27 (2H, m), 3.59 (0.5H, br s), 3.47 (1H, br s), 3.36 (0.5H, d, *J* = 3.5 Hz), 2.69 (2H, s), 2.60 (1H, dd, *J* = 14.4, 5.1 Hz), 2.43 (3H, m), 1.47 (3H, d, *J* = 1.8 Hz), 1.34 (3H, t, *J* = 7.2 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 176.3 (C), 176.2 (C), 151.2 (C), 151.1 (C), 147.9 (C), 147.5 (C), 147.0 (C), 126.4 (CH), 129.4 (CH), 123.5 (2) (CH), 99.7 (2) (CH), 99.0 (CH), 98.8 (CH), 73.9 (C), 73.8 (C), 71.3 (CH), 71.1 (CH), 61.9 (2) (CH₂), 43.8 (CH₂), 43.7 (CH₂), 43.5 (CH₂), 43.4 (CH₂), 26.1 (CH₃), 25.9 (CH₃), 20.9 (CH₂), 14.2 (CH₃). IR (film): 3466, 3126, 2984, 2838, 1718, 1604, 1520, 1347 cm⁻¹. HRMS (ESI) Calcd for C₁₉H₂₃NO₇ ([M+Na]⁺): 400.1367, found 400.1367.

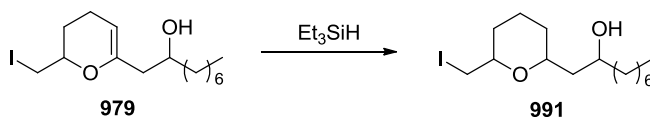


Pyran 989: *p*-Nitrobenzaldehyde (25 mg, 0.167 mmol) was added to a solution of enol ether **977** (59 mg, 0.139 mmol) in dry THF (0.178 mL) followed by 0.1 mL of a freshly prepared solution of ZnCl₂ (210 mg/mL, 0.139 mmol) in dry THF. The reaction was stirred at room temperature for 48 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO₂; hexanes:EtOAc, 3:1-1:1) to afford pyran **989** (40 mg, 51%) as a yellow oil. TLC: *R_f* = 0.33 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 8.20 (2H, d, *J* = 8.7), 7.68 (4H, m), 7.55 (2H, d, *J* = 8.7 Hz), 7.41 (6H, m), 5.02 (1H, m), 4.60 (2H, m), 4.17 (1H, m), 3.88 (2H, m), 3.48 (1H, m), 3.29 (1H, m), 2.70 (2H, d, *J* = 2.9 Hz), 2.47 (2H, m), 2.25 (2H, d, *J* = 6.1 Hz), 1.69 (2H, m), 1.06 (9H, s). ¹³C NMR (CDCl₃, 75 MHz): δ 151.2 (C), 148.6 (C), 147.6 (C), 147.1 (C), 135.5 (CH), 132.9 (C), 129.8 (CH), 127.8 (CH), 126.4 (2) (CH), 123.5 (CH), 99.2 (CH), 99.1 (CH), 98.0 (CH), 97.9 (CH), 70.9 (CH), 70.7 (CH), 69.4 (CH), 69.2 (CH), 63.0 (CH₂), 45.1 (CH₂), 43.7 (CH₂), 43.6 (CH₂), 41.3 (CH₂), 38.0 (CH₂), 26.8 (CH₃), 20.9 (CH₂), 19.0 (C). IR (film): 3396, 3072, 2931, 2858, 1717, 1603, 1522, 1346 cm⁻¹. HRMS (ESI) Calcd for C₃₃H₃₉NO₆Si ([M+Na]⁺): 596.2439, found 596.2437.

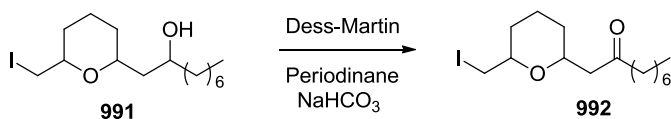


Pyran 990: *p*-Nitrobenzaldehyde (50 mg, 0.33 mmol) was added to a solution of enol ether **979** (70 mg, 0.276 mmol) in dry THF (0.1 mL) followed by 0.39 mL of a freshly prepared solution of ZnCl₂ (96 mg/mL, 0.276 mmol) in dry THF. The reaction was stirred at room temperature for 48 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO₂; hexanes:EtOAc, 3:1-1:1) to afford pyran **990** (59 mg, 53%) as a yellow oil. TLC: *R_f* = 0.32

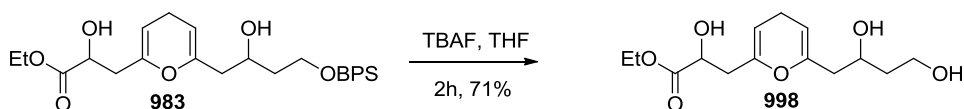
(hexanes:EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 8.19 (2H, d, $J = 8.7$ Hz), 7.53 (2H, d, $J = 8.5$ Hz), 4.98 (1H, m), 4.57 (2H, m), 3.75 (1H, m), 2.68 (2H, s), 2.40 (2H, m), 2.24 (1H, d, $J = 14.5$ Hz), 2.08 (1H, m), 1.45 (2H, m), 1.27 (10H, s), 10.77 (3H, t, $J = 7.0$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 151.1 (C), 151.0 (C), 148.7 (C), 147.5 (C), 147.4 (C), 147.1 (C), 126.4 (2) (CH), 123.5 (CH), 99.2 (CH), 98.1 (2) (CH), 71.0 (CH), 70.9 (CH), 69.7 (2) (CH), 43.5 (2) (CH_2), 41.1 (CH_2), 41.0 (CH_2), 37.0 (CH_2), 36.9 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 29.2 (CH_2), 25.6 (CH_2), 22.6 (CH_2), 20.9 (CH_2), 14.1. IR (film): 3401, 3080, 2928, 2856, 1603, 1521, 1346 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{31}\text{NO}_5$ ($[\text{M}+\text{Na}]^+$): 412.2094, found 412.2094.



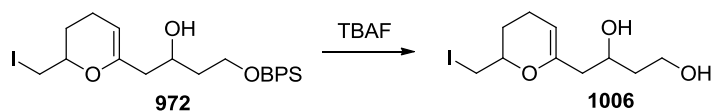
Tetrahydropyran 991: To a solution of iodide **979** (301mg, 0.79 mmol) in dichloromethane (1.3 mL) was added triethylsilane (0.10 mL, 0.796 mmol). The reaction mixture was cooled to -78°C and $\text{BF}_3\text{-EtO}_2$ (0.405 mL, 2.54 mmol) was added. The reaction was warmed to room temperature overnight and concentrated *in vacuo*. The resulting liquid was purified by flash column chromatography (SiO_2 ; hexanes:EtOAc, 5:1) to afford pyran **991** (193 mg, 64 %) as a yellow oil. TLC: $R_f = 0.73$ (hexanes:EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 3.93 (1H, m), 3.71 (1H, m), 3.38 (1H, m), 3.17 (2H, m), 2.88 (1H, br s), 1.53 (20 H, m), 0.88 (3H, t, $J = 6.7$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 77.3 (CH), 76.2 (CH), 68.8 (CH), 41.7 (CH_2), 37.1 (CH_2), 31.8 (CH_2), 31.2 (CH_2), 30.7 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 25.9 (CH_2), 23.2 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 10.1 (CH_2). IR (film): 3512, 2928, 2855 cm^{-1} .



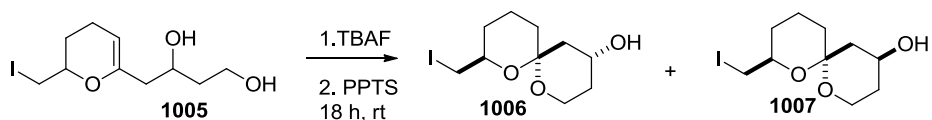
Tetrahydropyran 992: To a solution of tetrahydropyran **991** (30mg, 0.078 mmol) in dichloromethane (0.35 mL) was added Dess-Martin Periodinane (40 mg, 0.090mmol) and NaHCO₃ (10 mg, 0.26 mmol) at room temperature. The reaction stirred for 3 hr and was then diluted with diethyl ether (10 mL), filtered through a pad of celite, and concentrated *in vacuo*. The crude residue was purified by flash chromatography using deactivated silica gel (SiO₂; hexanes:EtOAc, 20:1) to afford tetrahydropyran **992** (19 mg, 66%) as a colorless oil. TLC: R_f = 0.63 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 3.82 (1H, m), 3.36 (1H, m), 3.13 (2H, m), 2.69 (1H, dd, *J* = 15.1, 7.9 Hz), 2.51 (2H, q, *J* = 7.4 Hz), 2.39 (1H, dd, *J* = 15.1, 4.8 Hz), 1.83 (2H, m), 1.59 (4H, m), 1.26 (10H, m), 0.88 (3H, t, *J* = 6.7 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 209.9 (C), 77.0 (CH), 75.0 (CH), 49.1 (CH₂), 44.2 (CH₂), 31.7 (CH₂), 31.0 (2) (CH₂), 29.1 (2) (CH₂), 23.5 (CH₂), 23.0 (CH₂), 22.6 (CH₂), 14.1 (CH₃), 9.6 (CH₂). IR (film): 2927, 2853, 1709 cm⁻¹.



Triol 998: TBAF (0.49mL of a 1M solution, 0.048 mmol) was added to a solution of silyl ether **983** (0.025g, 0.048 mmol) in THF (0.5 mL). The reaction was stirred for two hours at room temperature after which the reaction mixture was concentrated and run through a plug of silica (SiO₂; 2:1 (hexanes: EtOAc) – 10% MeOH in EtOAc). The crude residue was isolated as a yellow oil in 71% yield (0.010g) and quickly subjected to the next reaction. TLC: R_f = 0.09 (hexanes:EtOAc, 1:1). ¹H NMR (CDCl₃, 300 MHz): δ 4.62 (2H, m), 4.36 (1H, m), 4.27 (2H, dq, *J* = 7.2, 0.9 Hz), 4.08 (1H, t, *J* = 6.9 Hz), 3.87 (2H, m), 2.70 (2H, s), 2.64-2.38 (2H, m), 2.29 (2H, m), 1.73 (2H, m), 1.41 (3H, t, *J* = 7.1 Hz).

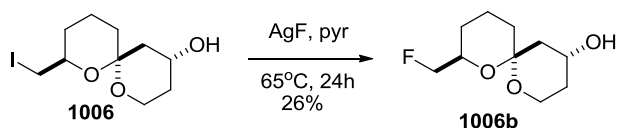


Diol **1006**: TBAF (0.184 mL of a 1 M solution, 0.184 mmol) was added to a solution of silyl ether **972** (0.100 g, 0.182 mmol) in THF (1.9 mL). The reaction was stirred for two hours at room temperature after which the reaction mixture was concentrated and run through a plug of silica (SiO₂; 2:1 (hexanes: EtOAc) – 10% MeOH in EtOAc). The crude residue was isolated as a yellow oil in 72% yield (0.041 g) and quickly subjected to the next reaction. TLC: R_f = 0.11 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 4.61 (1H, m), 4.10 (1H, m), 3.87 (3H, m), 3.32 (2H, m), 2.97 (1H, d, J = 3.1 Hz), 2.90 (1H, d, J = 3.1 Hz), 2.66 (1H, m), 2.24 (2H, m), 2.04 (3H, m), 1.72 (2H, m).

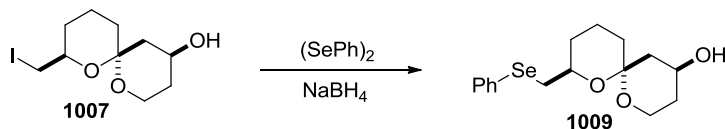


Spiroketal 1006 and 1007: TBAF (0.184 mL) was added to a solution of dihydropyran **1005** dissolved in THF (1.9 mL). The reaction was stirred for two hours at room temperature. The solution was concentrated and subjected to the next reaction. PPTS (2 mg, 0.009 mmol) was added to the concentrate, which was diluted with CH₂Cl₂ (1.0 mL). The reaction was stirred at room temperature overnight and concentrated afterwards. Purification via column chromatography (SiO₂; hexanes:EtOAc, 9:1-2:1) afforded spiroketal **1006** (14 mg) and spiroketal **1007** (14 mg), colorless oils, as a 1:1 mixture of separable diastereomers. Spiroketal **1006**: TLC: R_f = 0.22 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 4.25 (1H, m), 3.87 (1H, ddd, J = 12.8, 11.4, 2.3 Hz), 3.68 (2H, m), 3.20 (1H, dd, J = 10.2, 3.7 Hz), 3.10 (1H, dd, J = 10.2, 8.9 Hz), 2.05 (1H, ddd, J = 12.4, 4.7, 2.1 Hz), 1.85 (3H, m), 1.60 (3H, m), 1.45 (1H, dq, J = 13.2, 4.9

Hz), 1.34 (1H, dd, $J = 12.4, 11.2$), 1.19 (1H, ddq, $J = 12.4, 4.7, 1.5$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 98.4 (C), 69.3 (CH), 64.1 (CH), 59.1 (CH_2), 45.0 (CH_2), 35.0 (CH_2), 34.6 (CH_2), 30.8 (CH_2), 18.6 (CH_2), 9.8 (CH_2). IR (film): 3394, 2943, 1090 cm^{-1} . Spiroketal **1007**: TLC: $R_f = 0.46$ (hexanes:EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 4.15 (1H, dt, $J = 12.1, 3.3$ Hz), 4.05 (1H, m), 3.79 (1H, m), 3.64 (1H, m), 3.22 (1H, dd, $J = 10.4, 2.9$ Hz), 3.08 (1H, dd, $J = 10.2, 10.1$ Hz), 1.88 (2H, m), 1.76 (3H, m), 1.67 (1H, dd, $J = 14.3, 2.9$ Hz), 1.56 (2H, m), 1.41 (1H, dt, $J = 13.5, 4.7$ Hz), 1.21 (1H, m). ^{13}C NMR (CDCl_3 , 75 MHz): δ 98.4 (C), 70.4 (CH), 64.3 (CH), 55.5 (CH_2), 40.2 (CH_2), 34.7 (CH_2), 32.0 (CH_2), 30.7 (CH_2), 18.2 (CH_2), 9.3 (CH_2). IR (film): 3524, 2940, 1081 cm^{-1} .

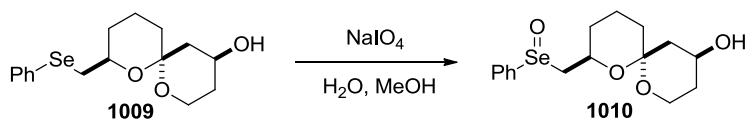


Fluoride **1006b**: To a solution of spiroketal **1006** (0.072g, 0.231 mmol) in pyridine (3 mL) was added AgF (0.088g, 0.692 mmol). The reaction was stirred at 65°C for 24 hours in the dark. The reaction mixture was concentrated in vacuo and purified by column chromatography (SiO_2 ; hexanes:EtOAc, 6:1-2:1), which afforded the fluoride (12 mg, 26%) as a colorless oil. TLC: $R_f = 0.18$ (hexanes:EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ 4.41 (1H, d, $J = 3.5$ Hz), 4.27 (1H, d, $J = 3.5$ Hz), 4.16 (1H, m), 3.85 (1H, m), 3.67 (2H, m), 2.06 (1H, m), 1.90 (1H, m), 1.74-1.25 (8H, m).



Spiroketal 1009: Iodide **1007** was dissolved in ethanol and THF (5:3, 2.5 mL) and cooled to 0°C. Diphenylselenide (38 mg, 0.123 mmol) and sodium borohydride (8 mg, 0.224 mmol) were

added to the reaction mixture. The reaction was allowed to warm to room temperature overnight after which it was concentrated *in vacuo*. Purification via column chromatography (SiO₂; hexanes:EtOAc, 15:1-8:1) afforded spiroketal **1009** (33 mg, 87%) as a colorless oil. TLC: R_f = 0.50 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 7.50 (2H, m), 7.25 (3H, m), 4.19 (1H, d, J = 10.8 Hz), 4.02 (2H, m), 3.81 (1H, m), 3.81 (1H, m), 3.54 (1H, dd, J = 11.6, 4.9 Hz), 3.08 (1H, dd, J = 12.5, 3.6 Hz), 2.89 (1H, dd, J = 12.5, 9.8 Hz), 1.73 (8H, m), 1.34 (2H, m). ¹³C NMR (CDCl₃, 75 MHz): δ 132.2 (CH), 130.1 (C), 129.1 (CH), 126.8 (CH), 98.1 (C), 68.7 (CH), 64.3 (CH), 55.2 (CH₂), 40.3 (CH₂), 34.7 (CH₂), 33.5 (CH₂), 32.0 (CH₂), 31.0 (CH₂), 18.2 (CH₂). IR (film): 3505, 3056, 2937, 2878, 1655 cm⁻¹.



Spiroketal 1010: Spiroketal **1009** was dissolved in a mixture of methanol and dionized water (6:1, 1.5 mL). To this solution was added NaHCO₃ (9 mg, 0.106 mmol) and NaIO₄ (27 mg, 0.126 mmol). The reaction was stirred at room temperature for four hours after which a white precipitate formed. Methanol was evaporated and the resulting liquid was partitioned between dichloromethane (10 mL) and water (5 mL). The two layers were separated and the water layer was extracted using dichloromethane (3 x 15 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated *in vacuo*. The resulting solid white product (34 mg, 100%) was used without further purification in the reaction sequence. TLC: R_f = 0.26 (hexanes:EtOAc, 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 7.74 (2H, m), 7.50 (3H, m), 4.29 (2H, m), 4.06 (1H, m), 3.70 (1H, m), 2.92 (2H, m), 2.05-1.29 (10H, m).

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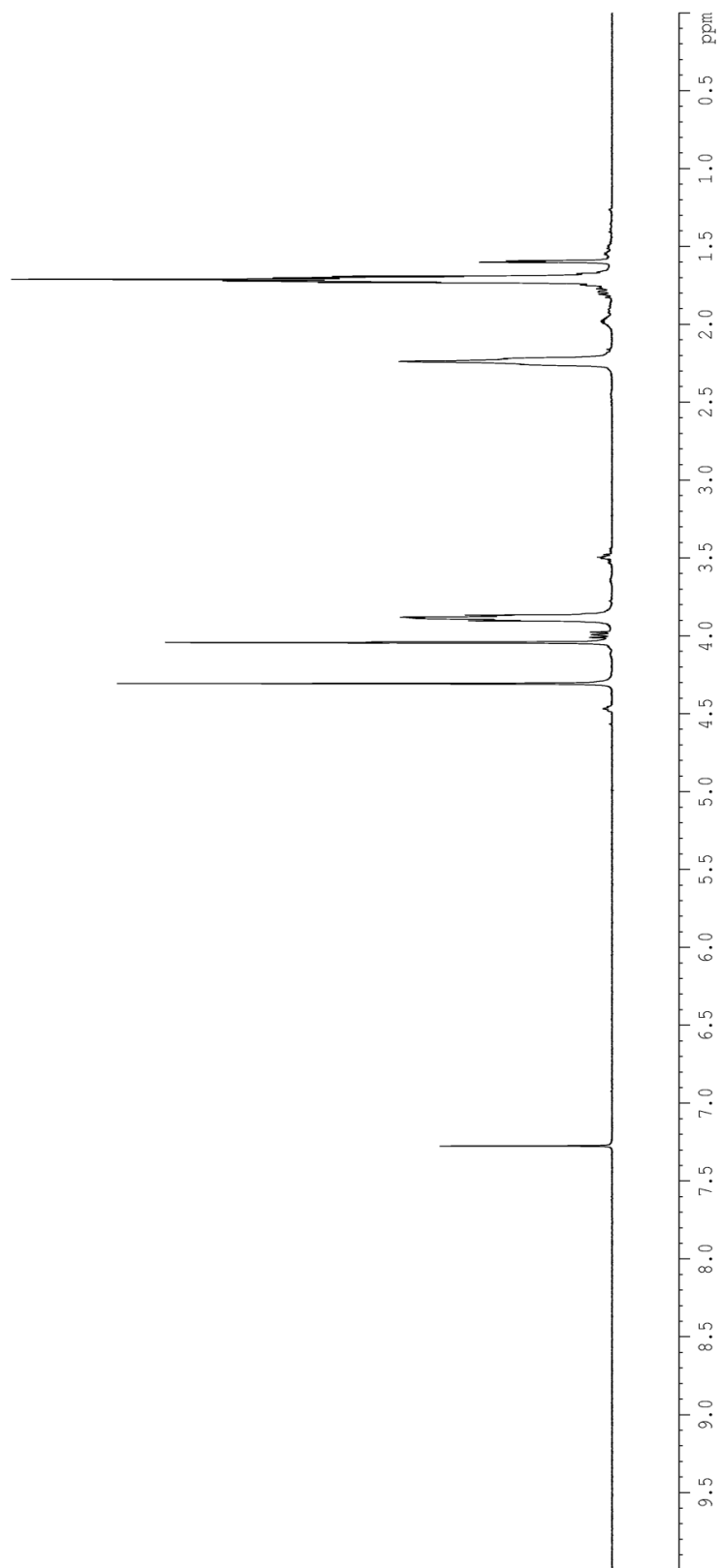
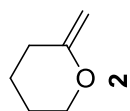
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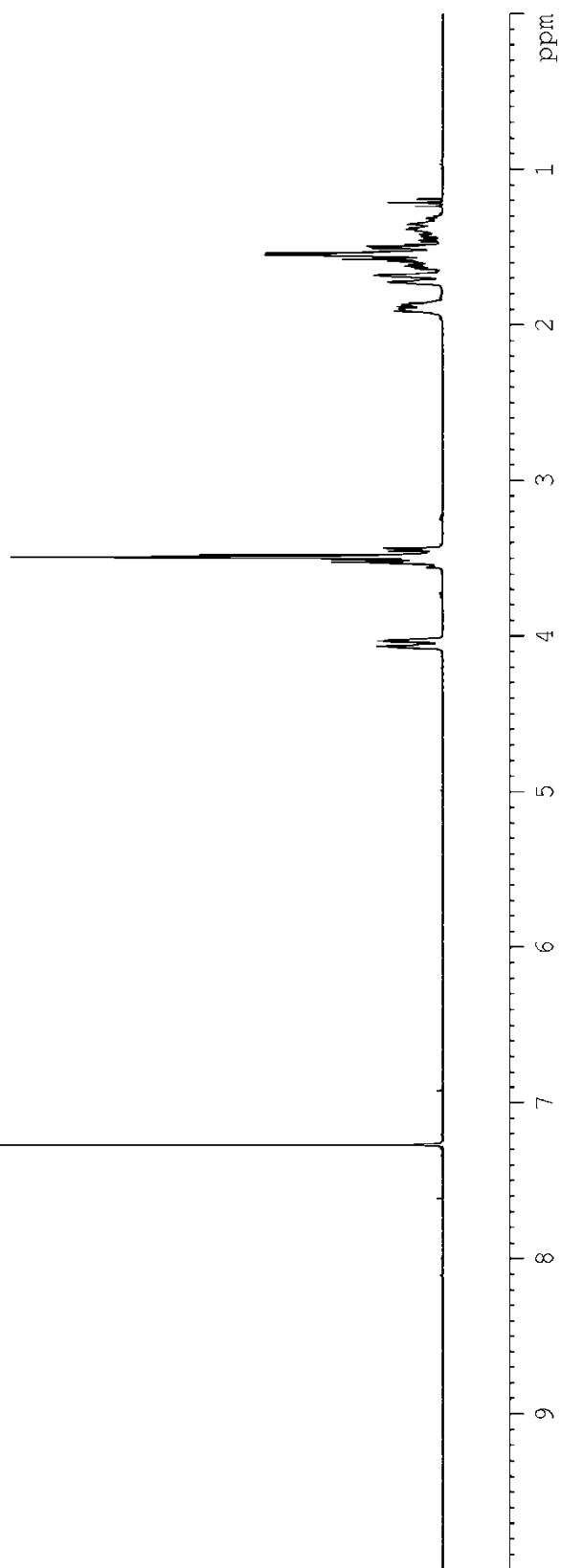
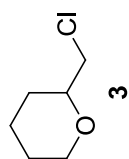
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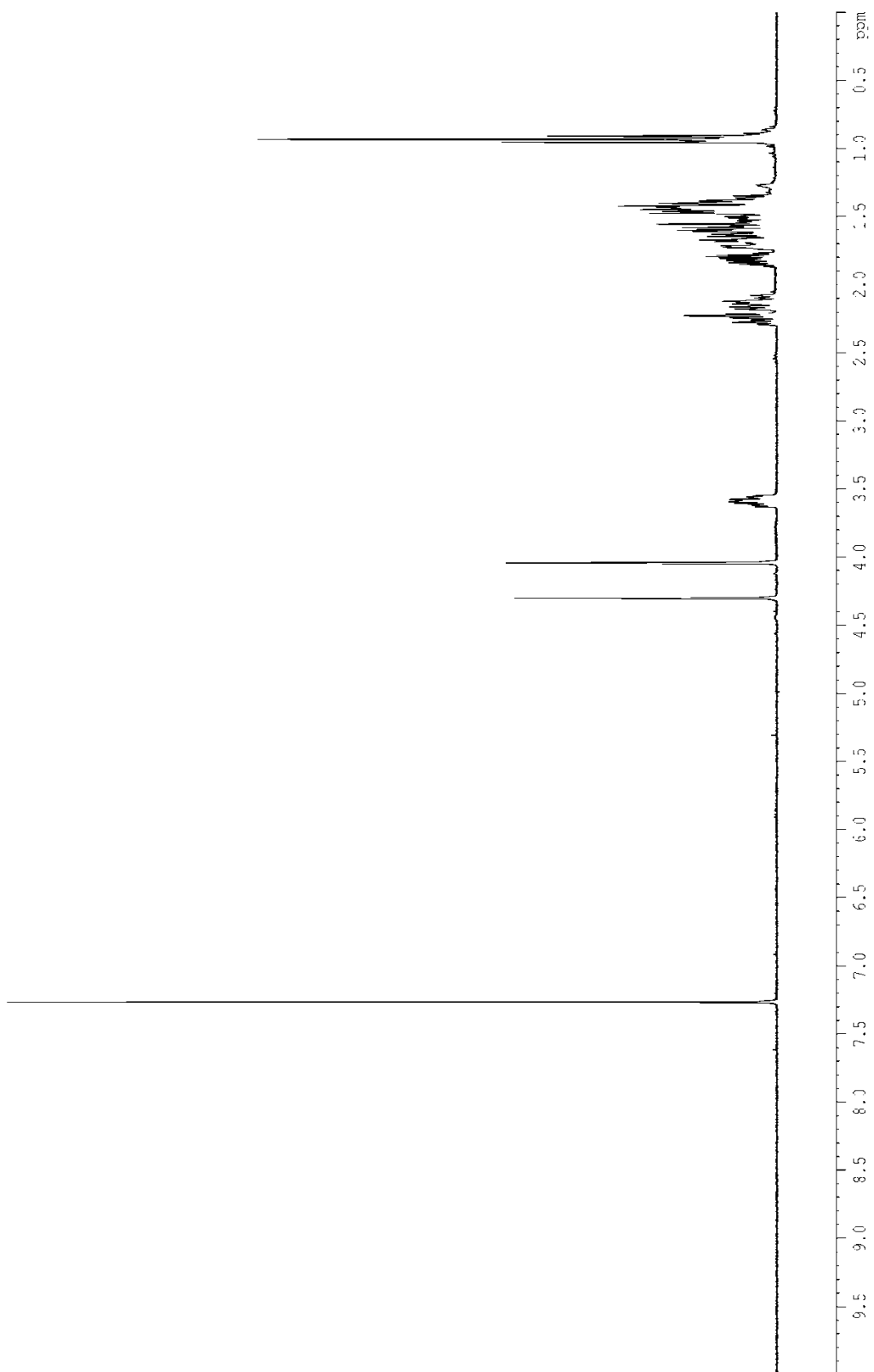
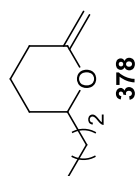
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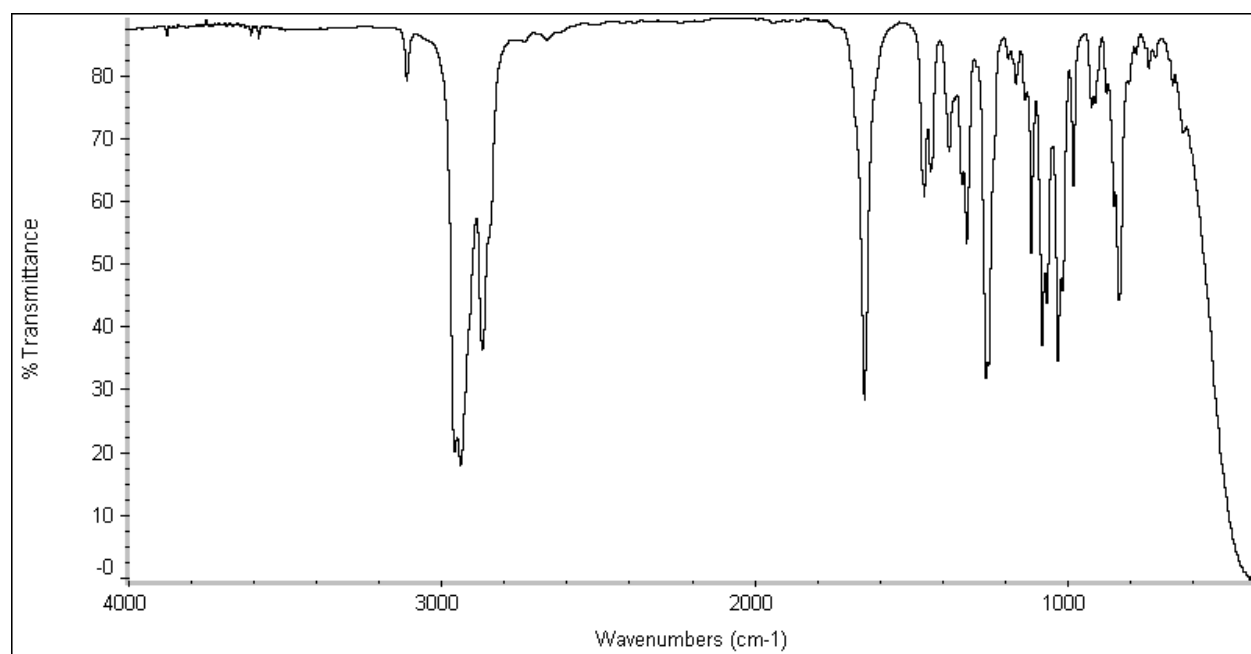
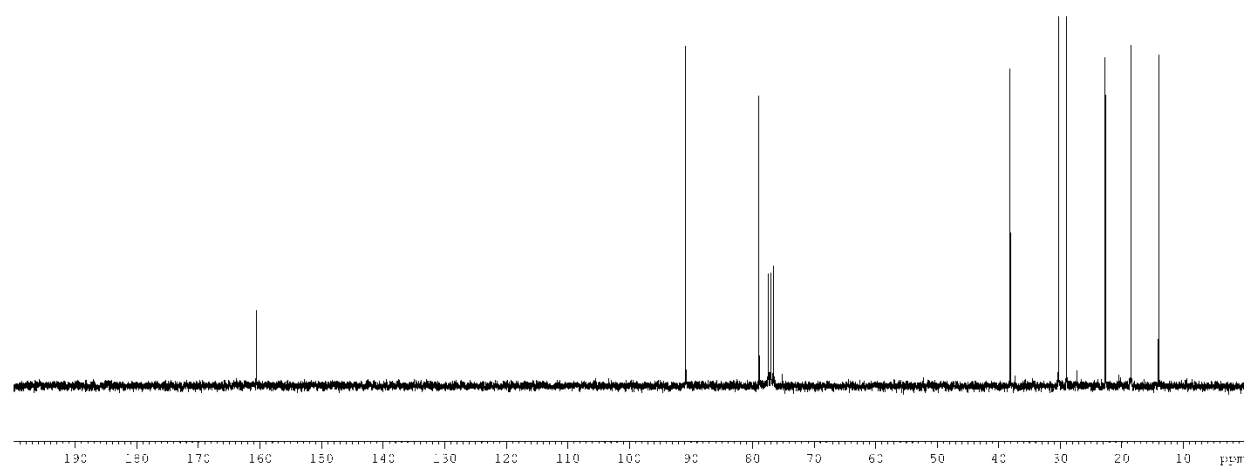
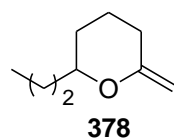
Appendix 1

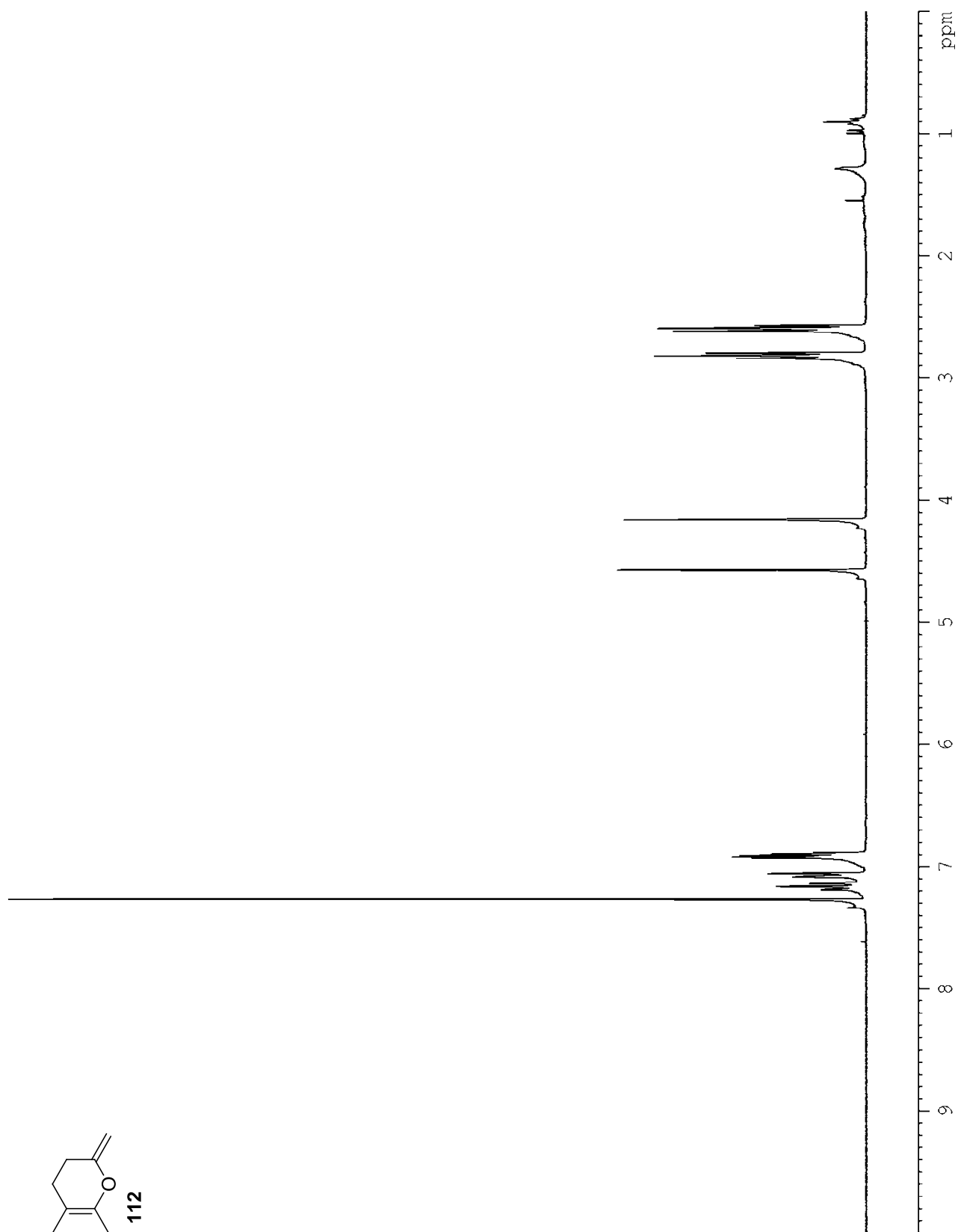
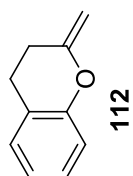
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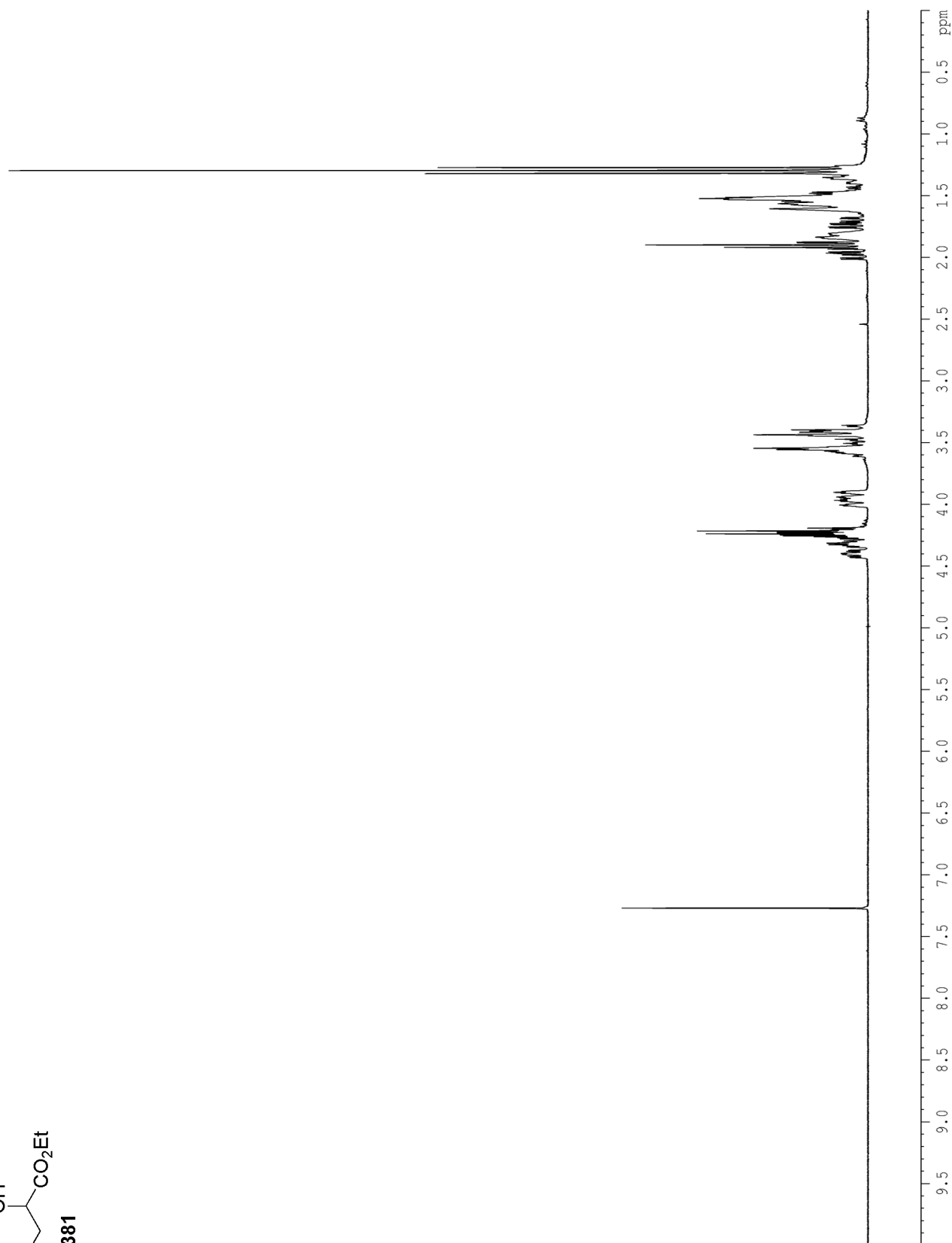
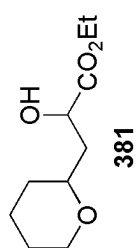


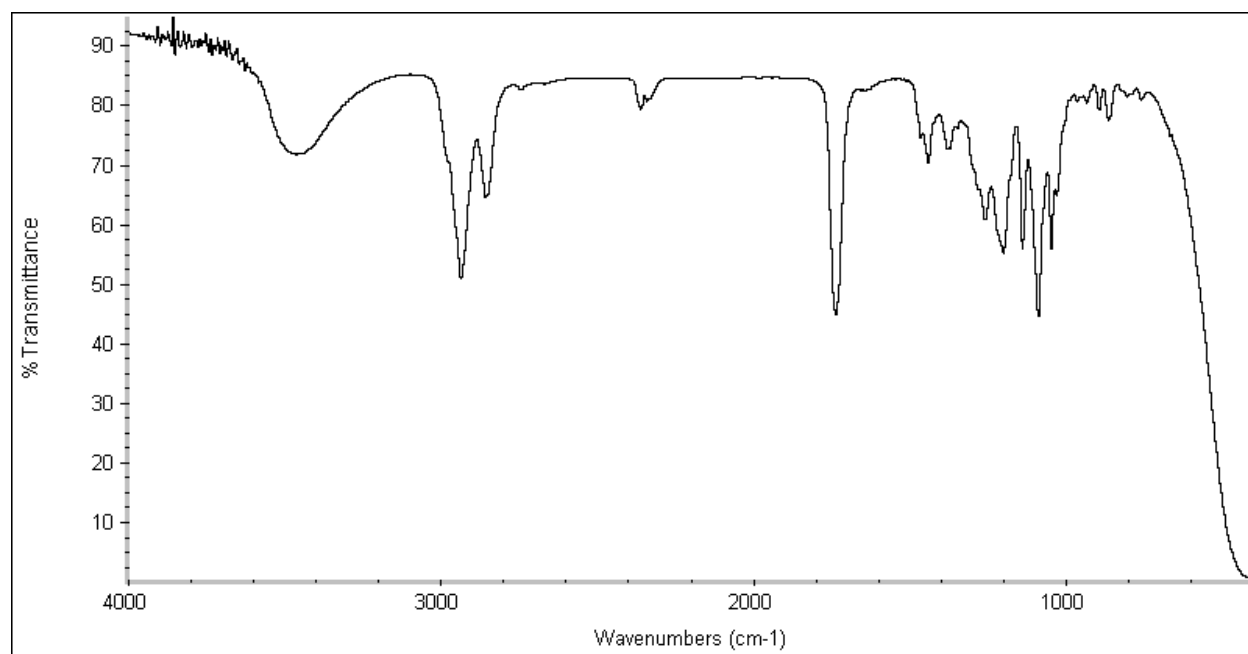
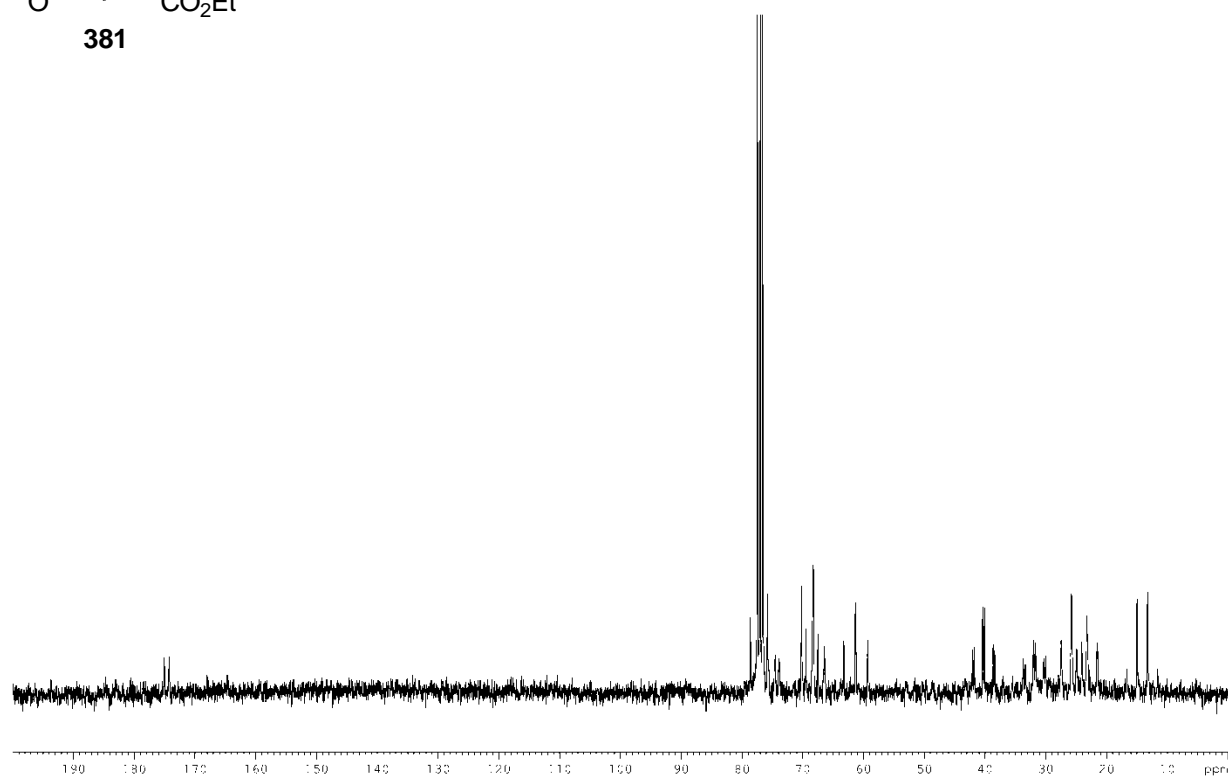
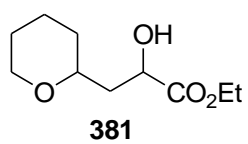


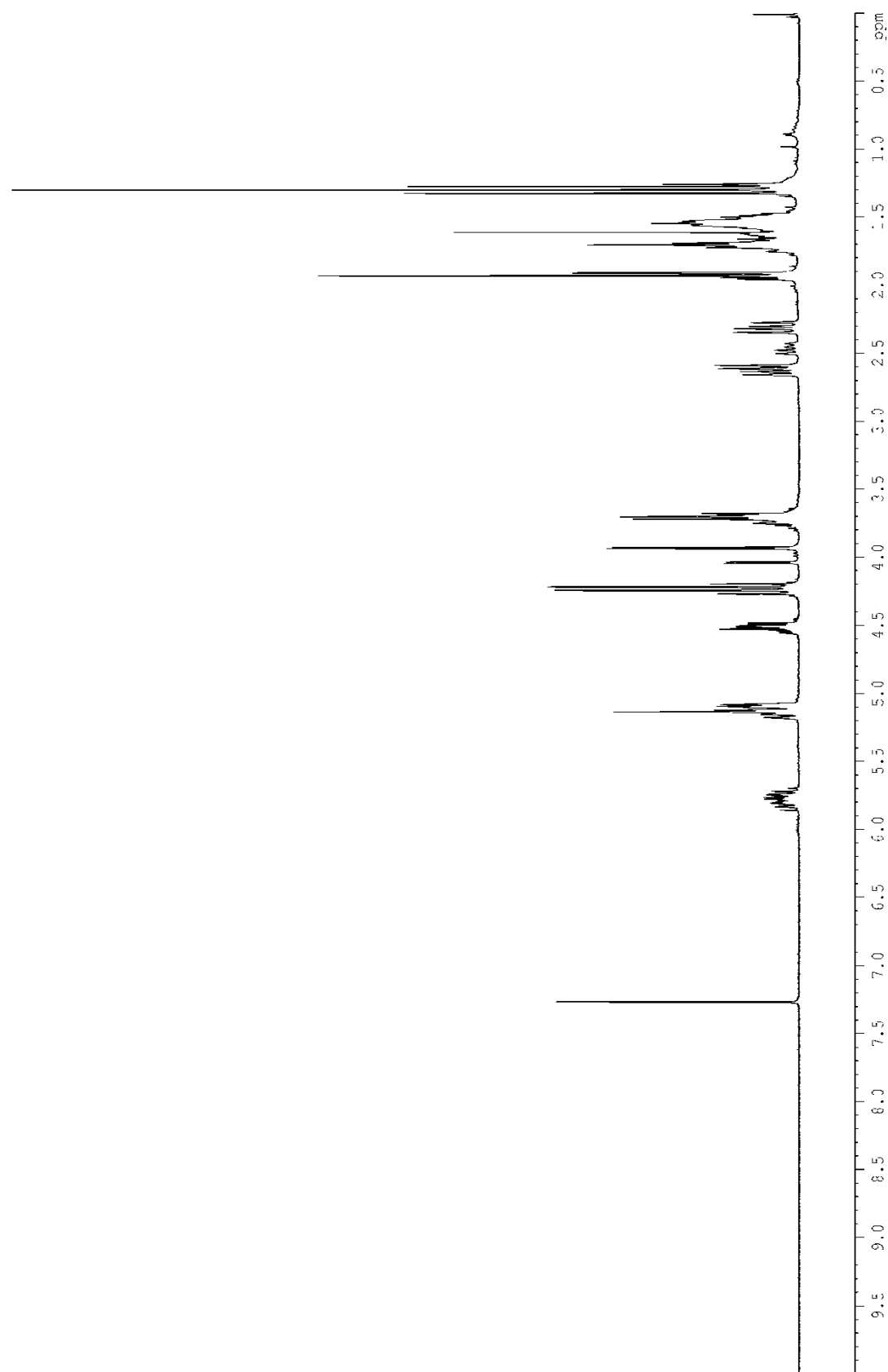
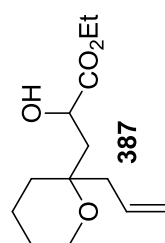


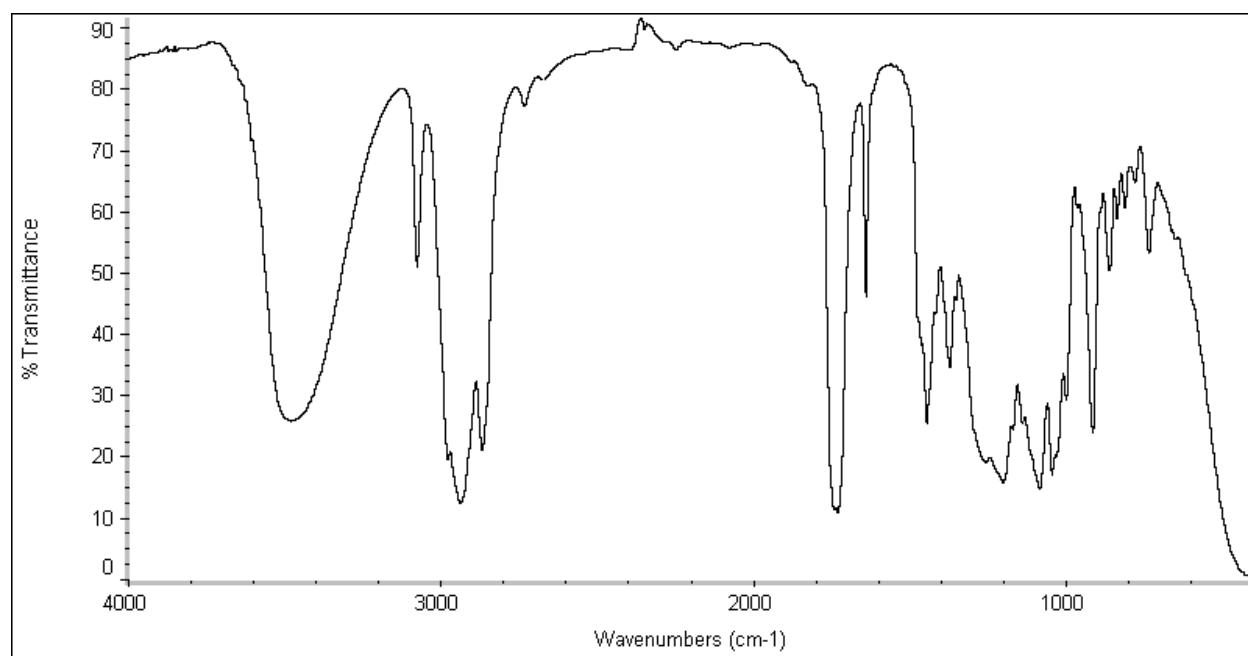
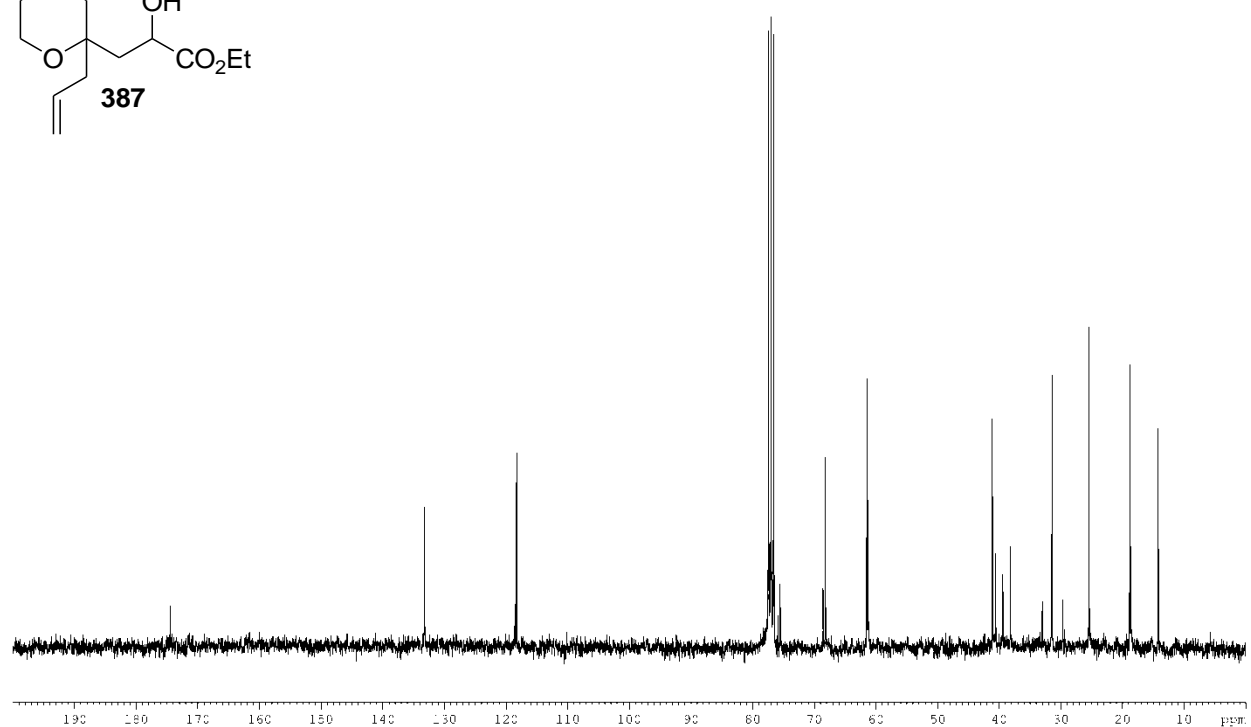
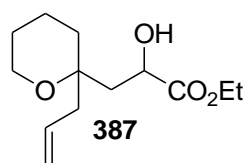


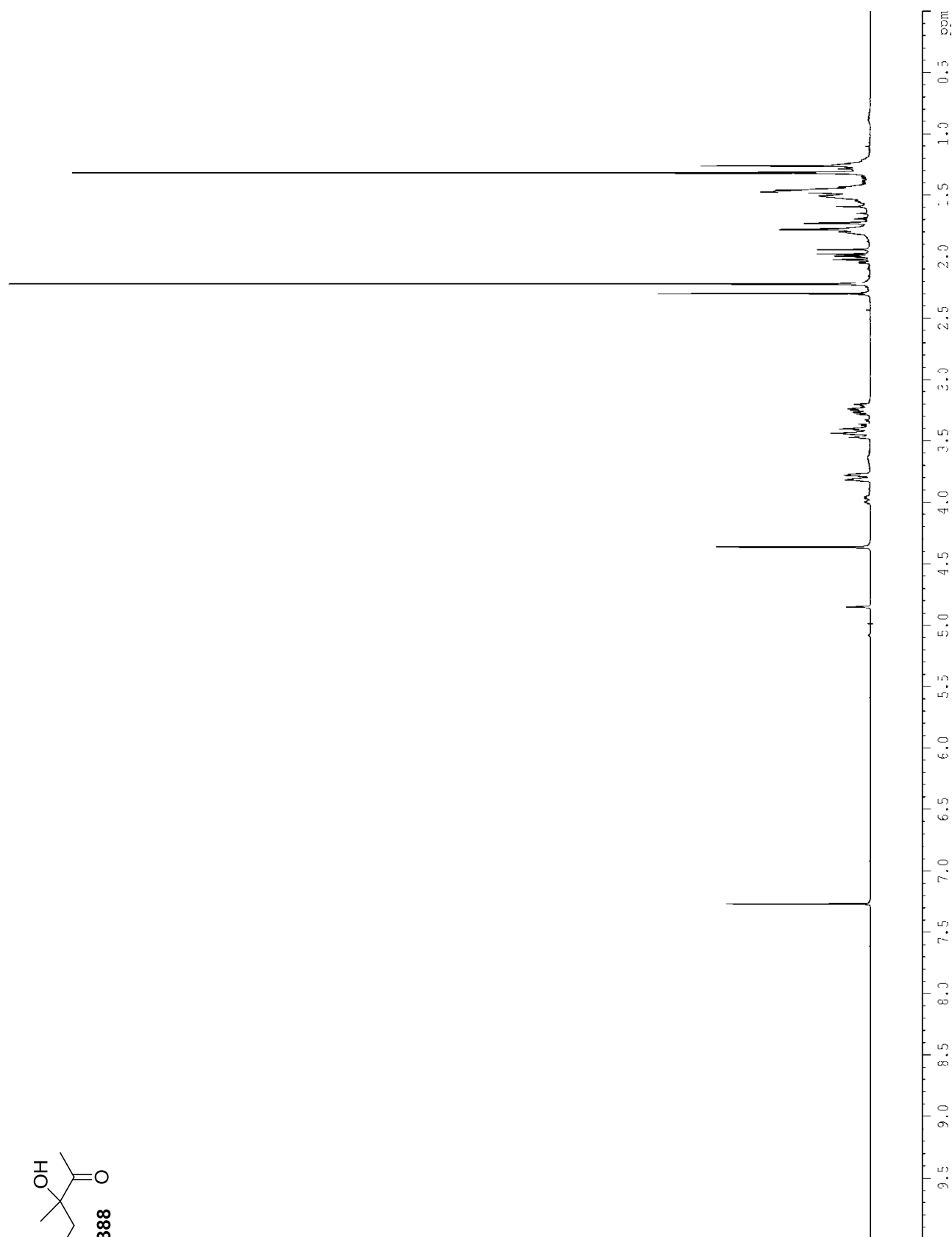
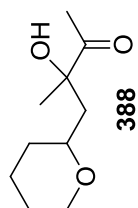


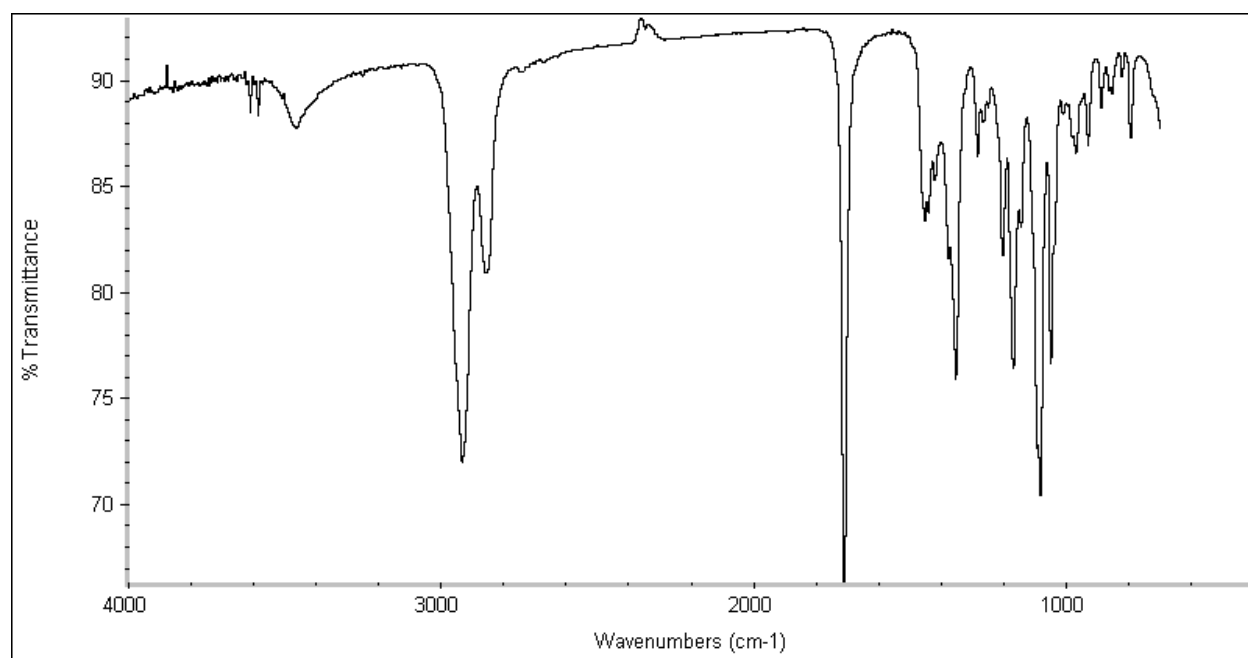
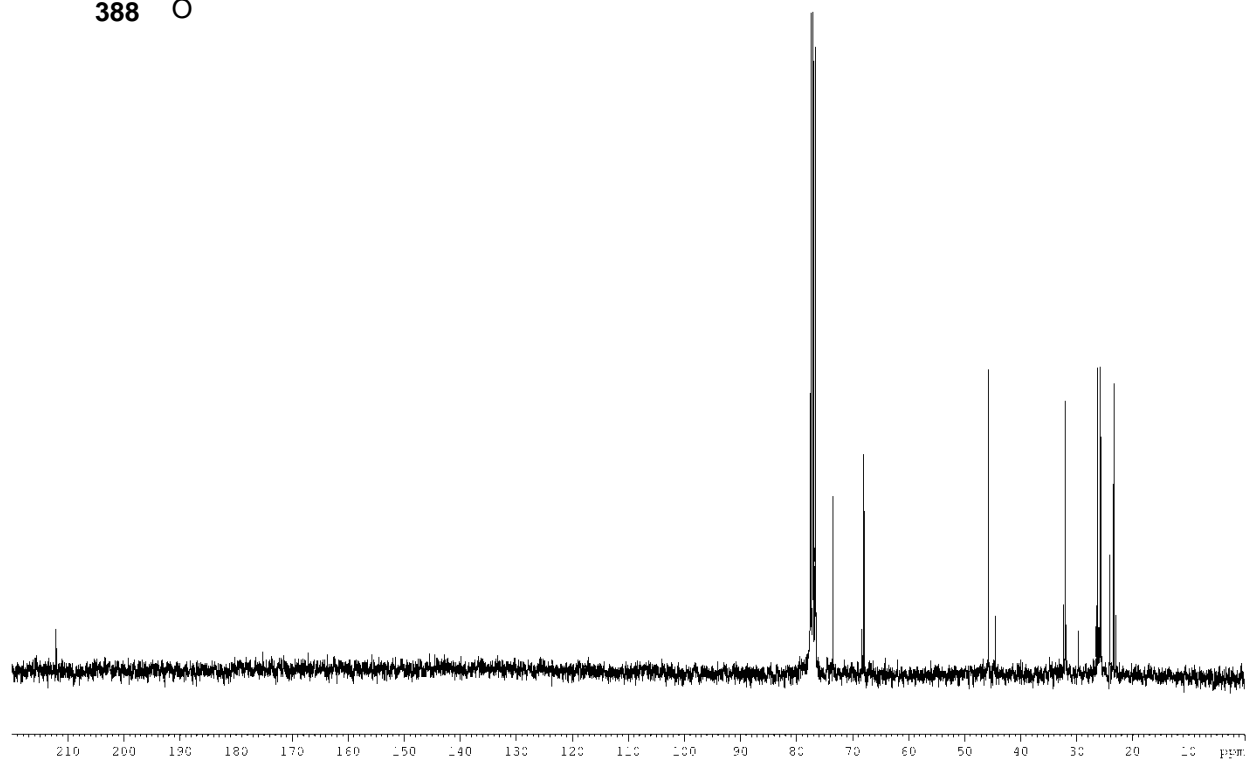
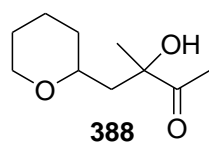


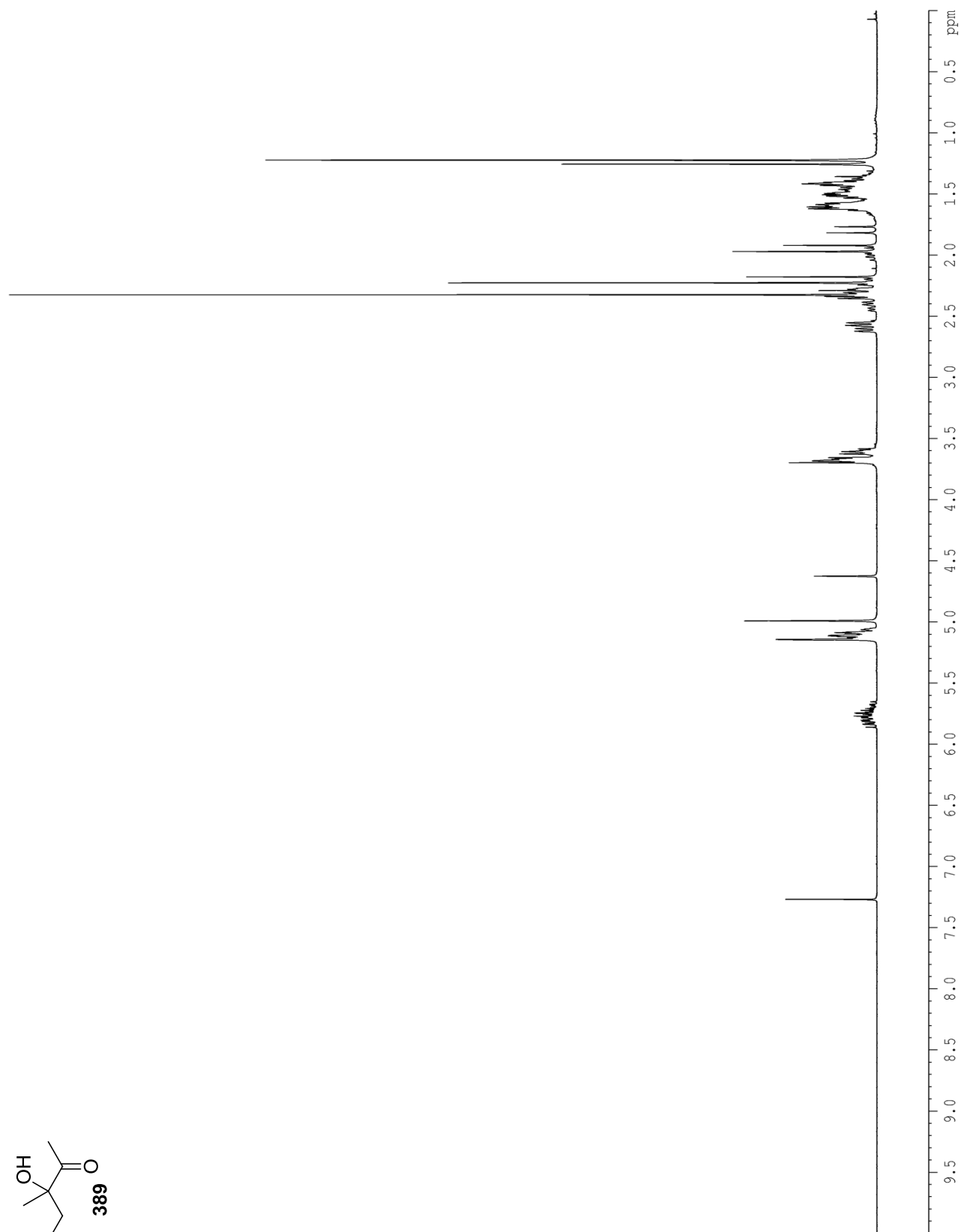
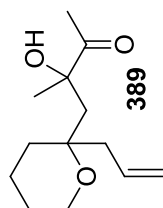


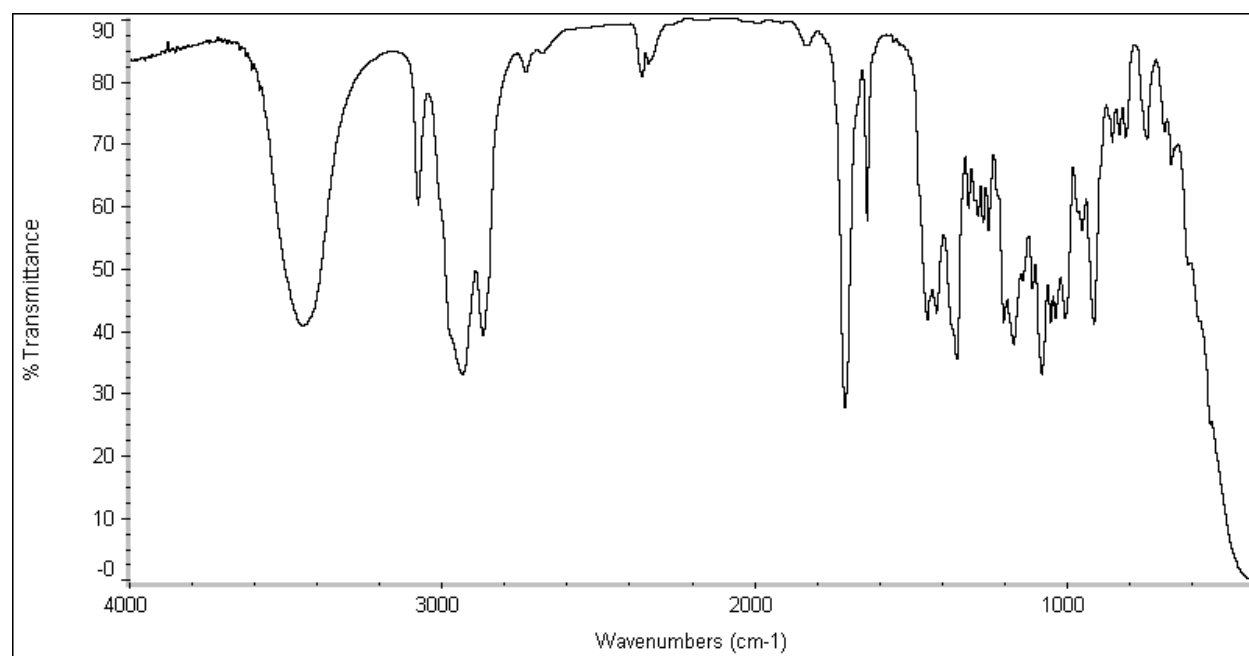
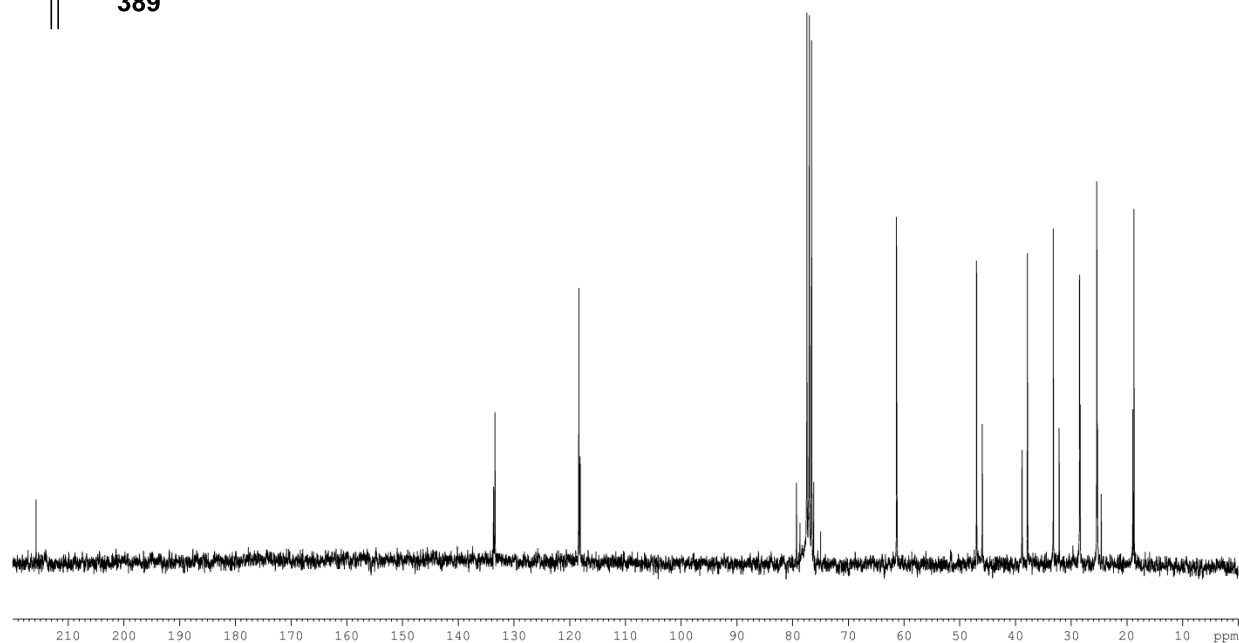
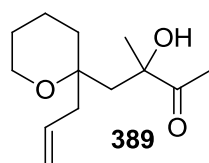


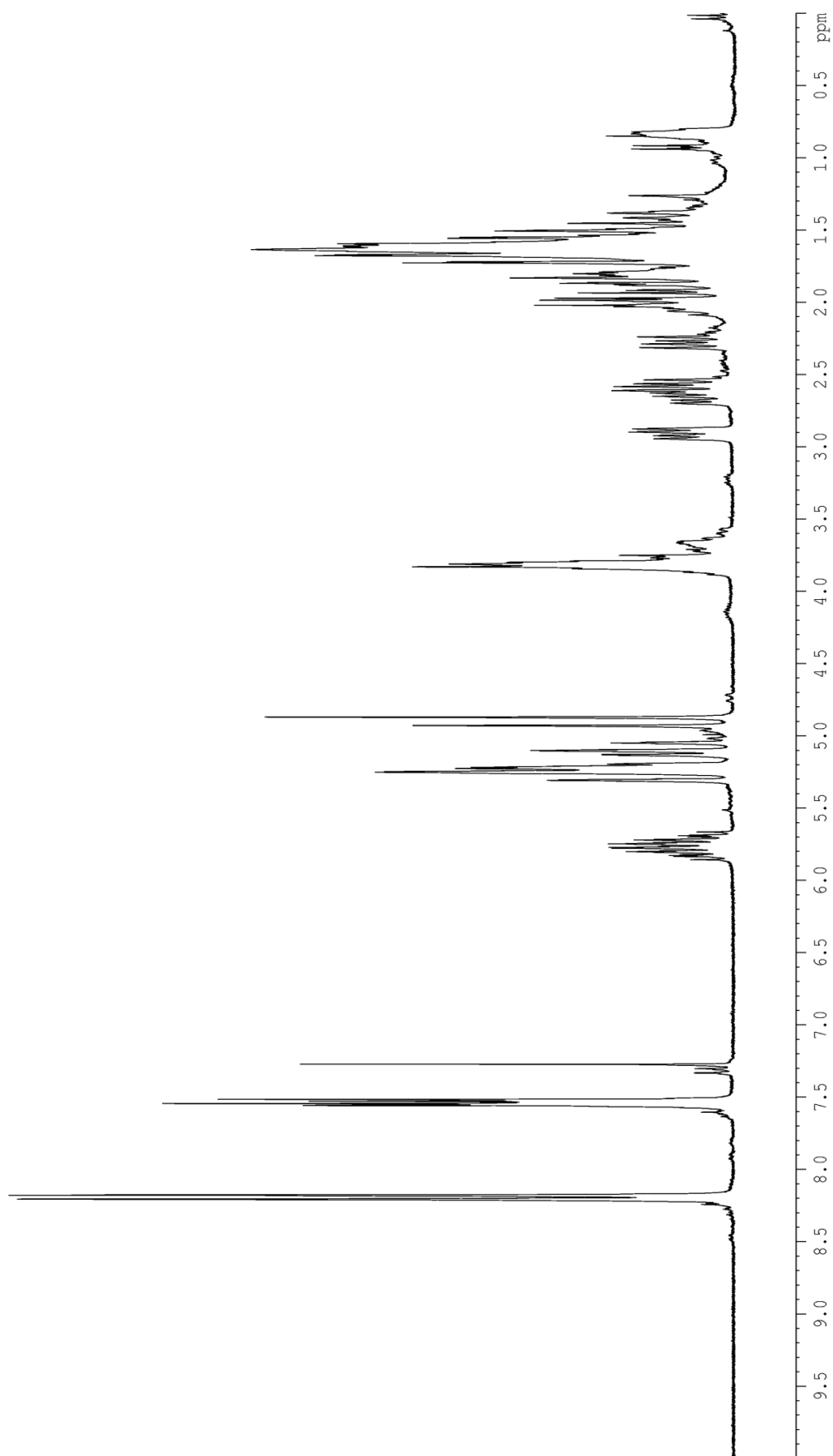
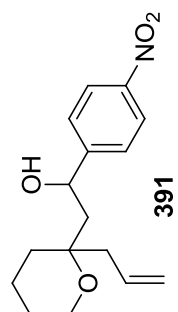


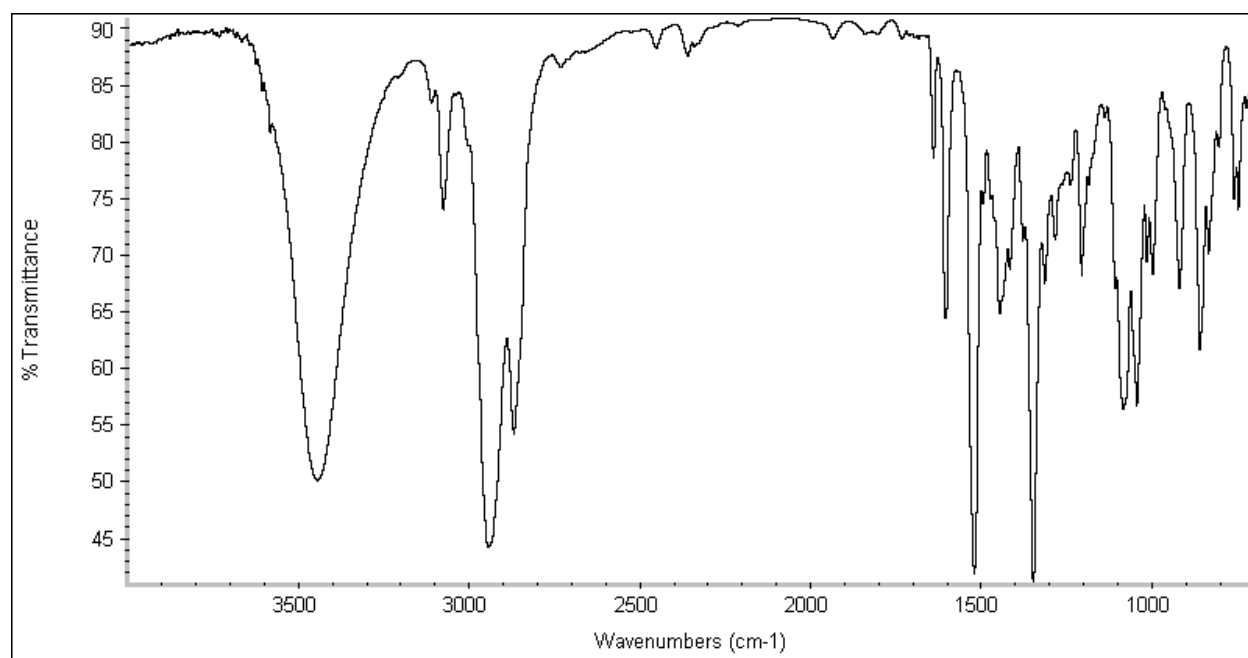
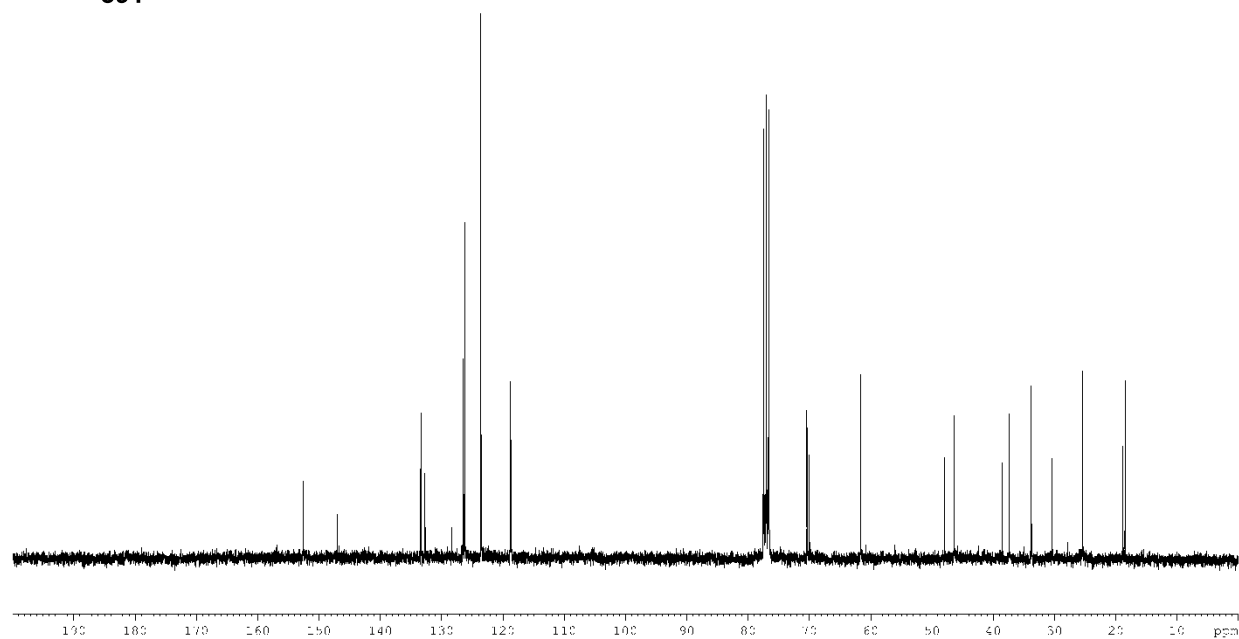
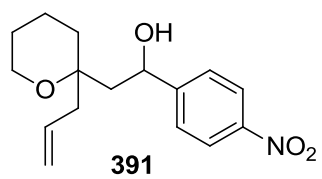


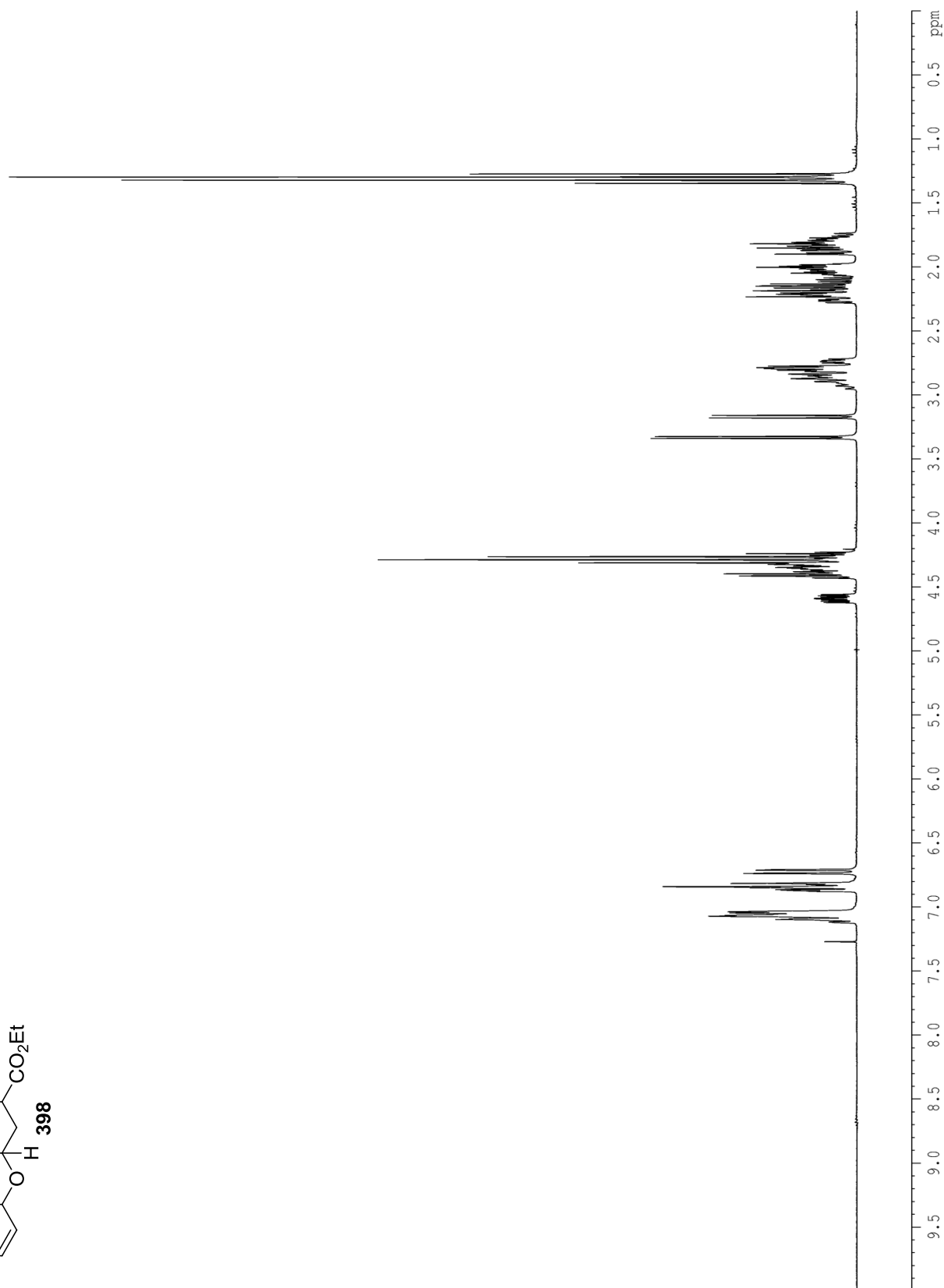
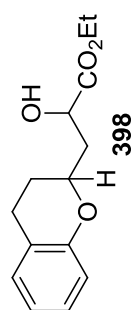


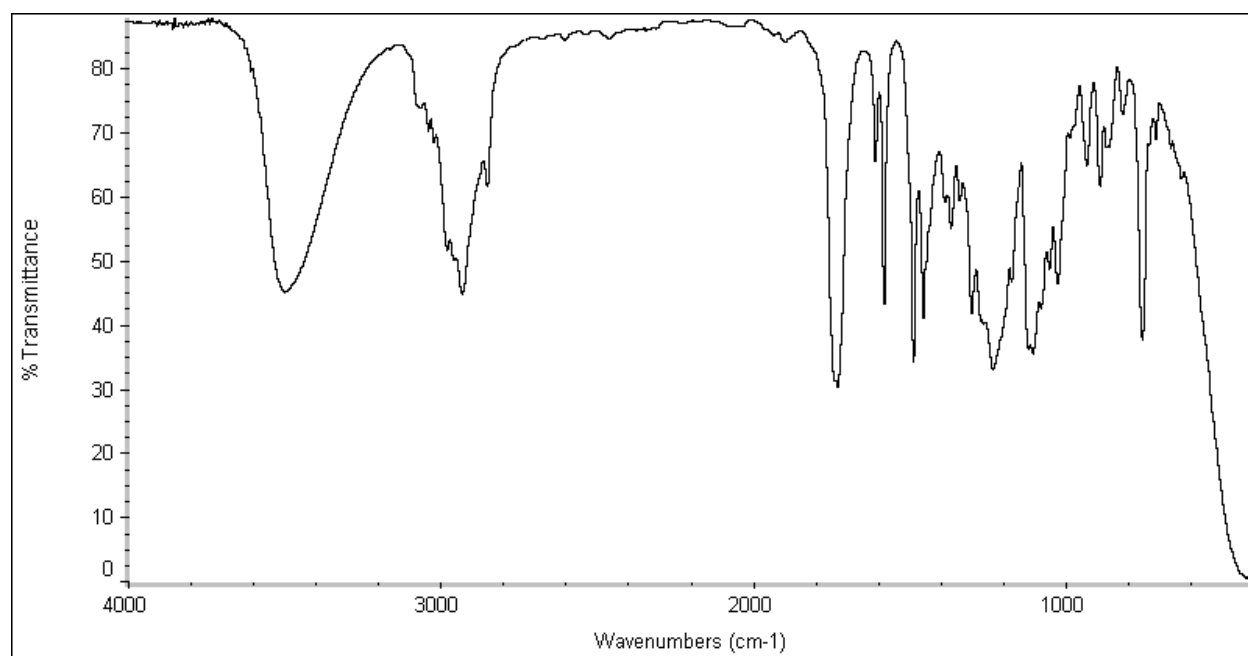
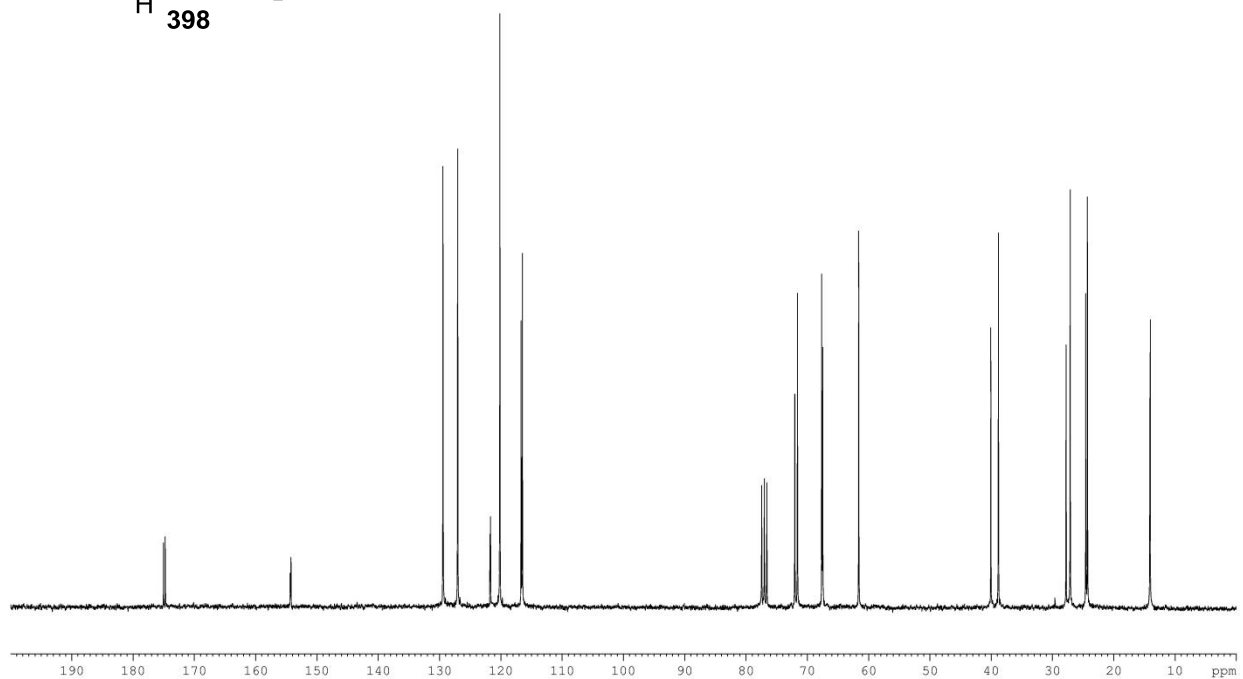
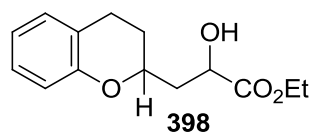


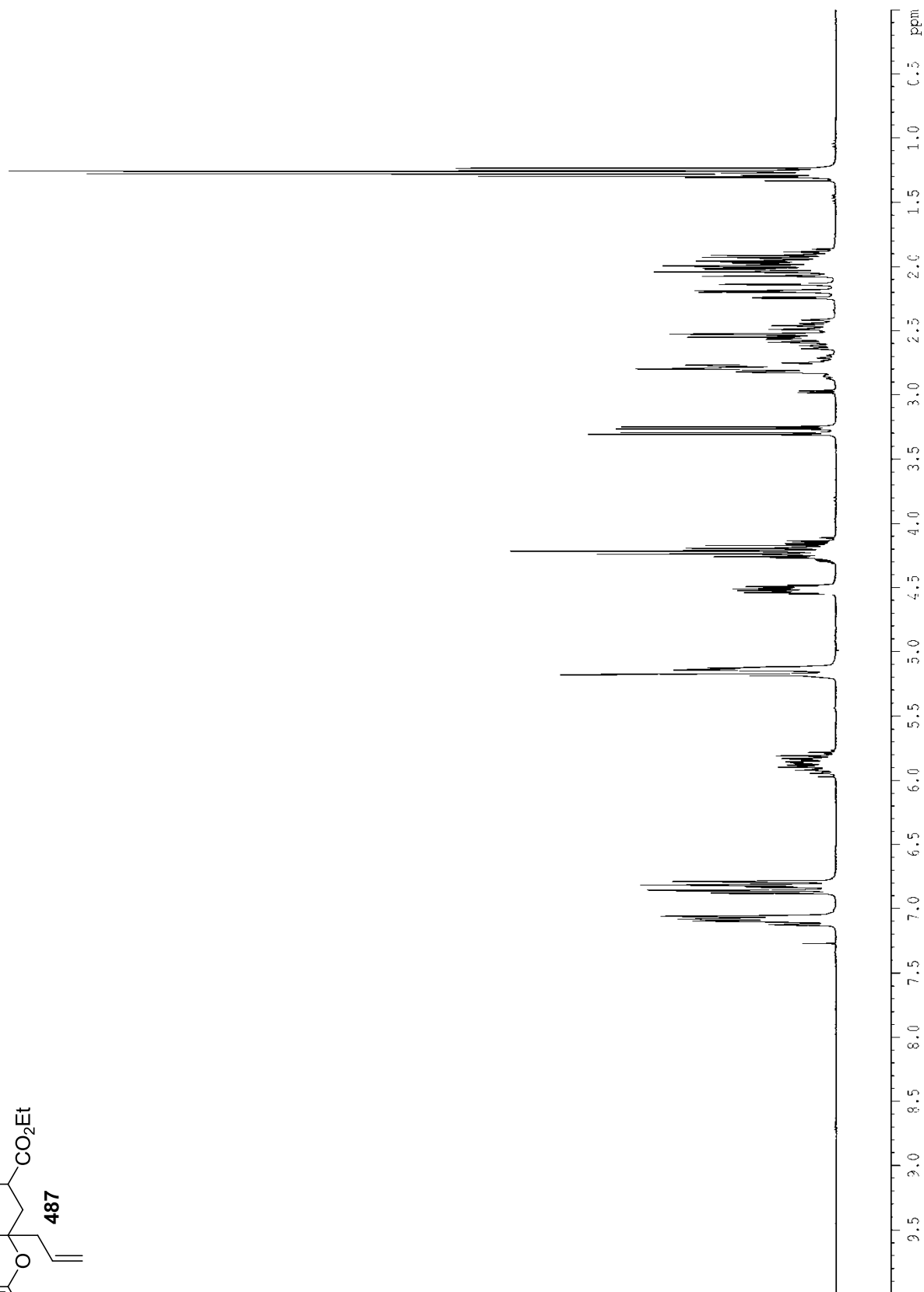
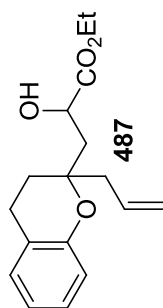


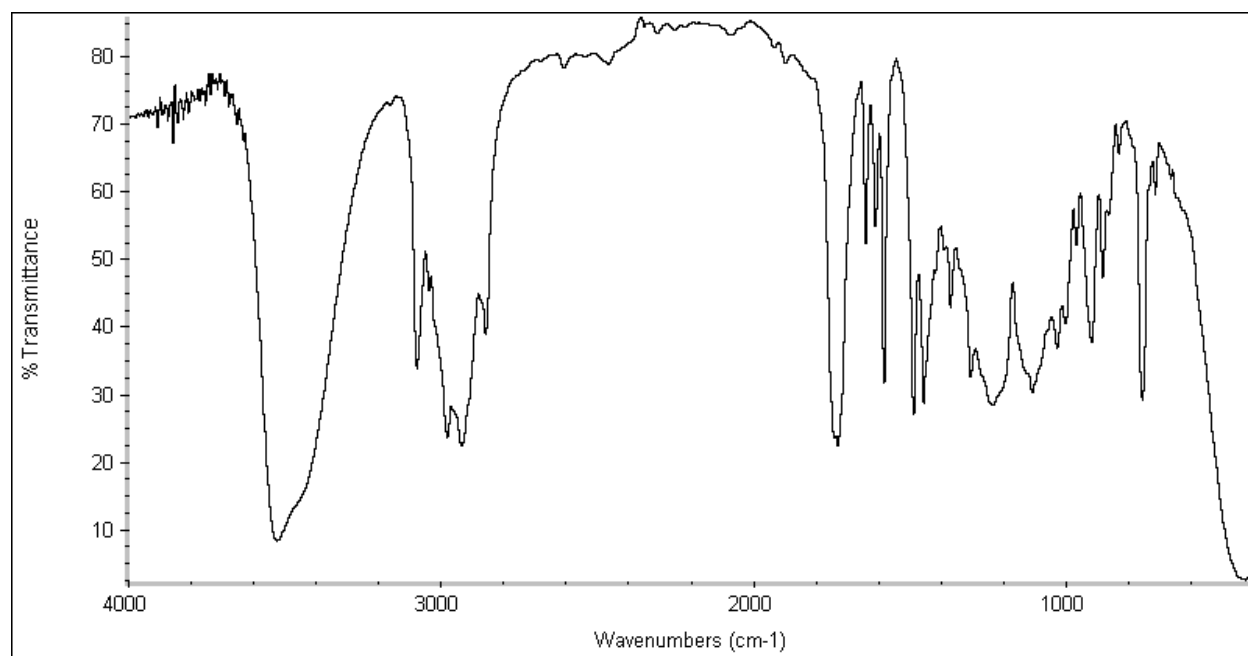
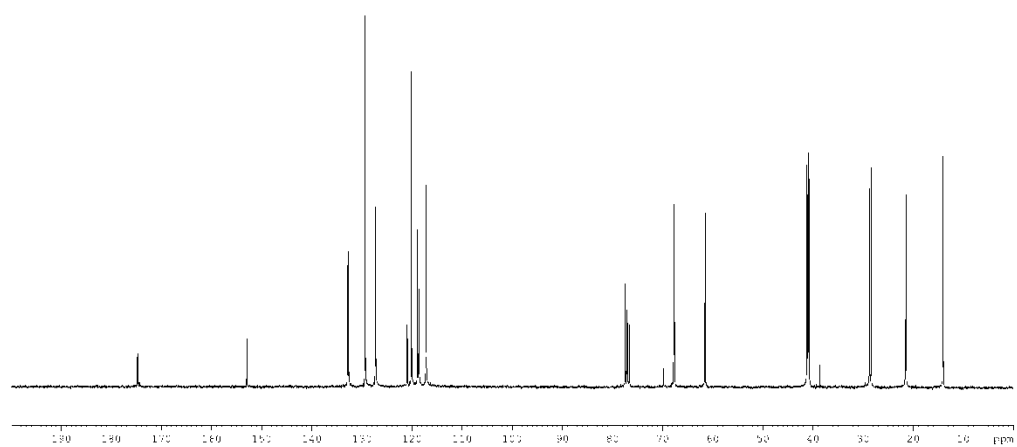
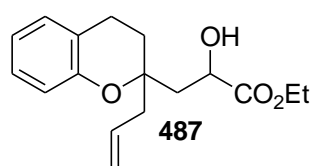


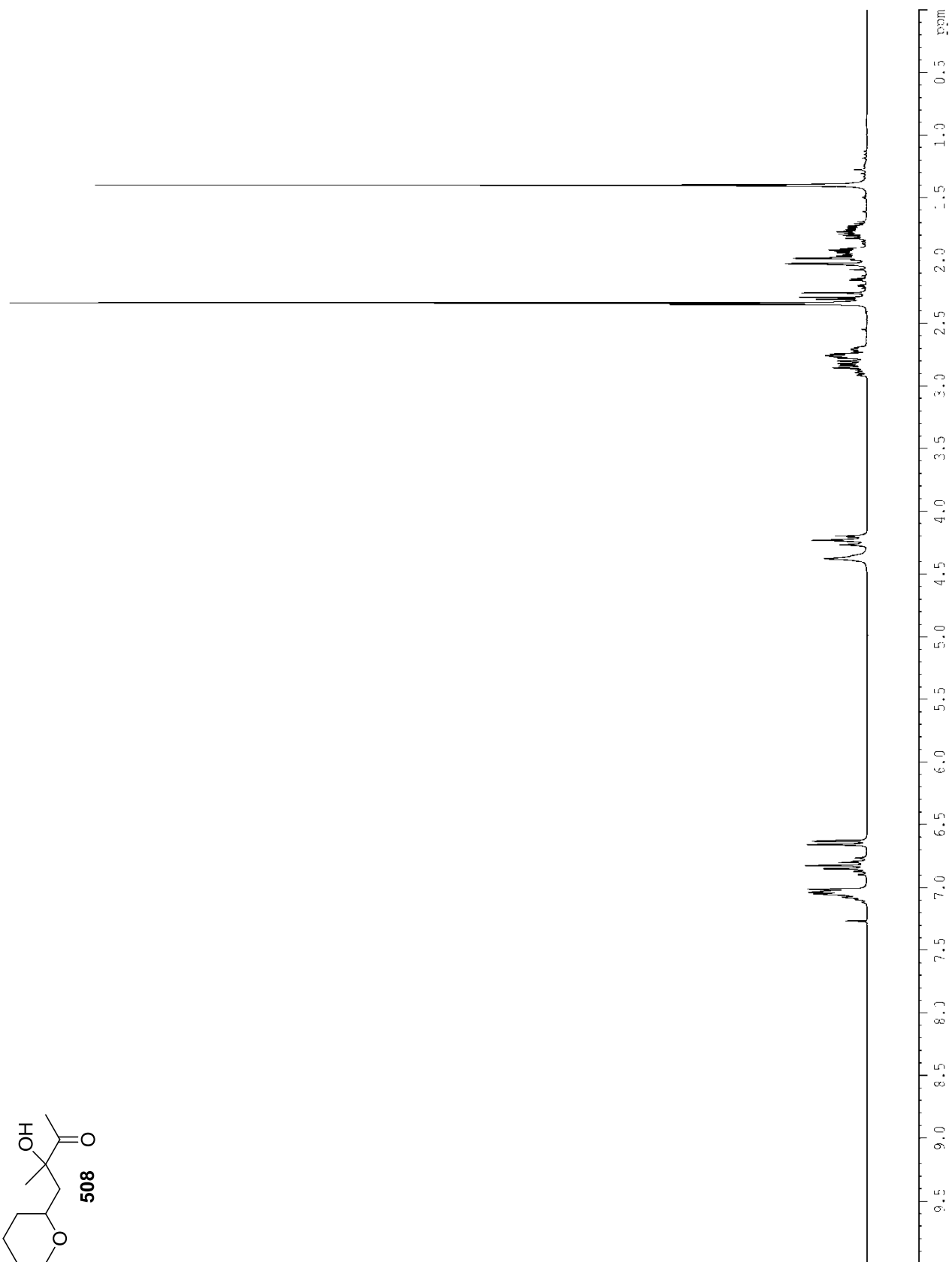
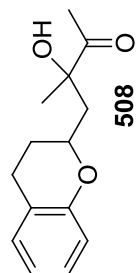


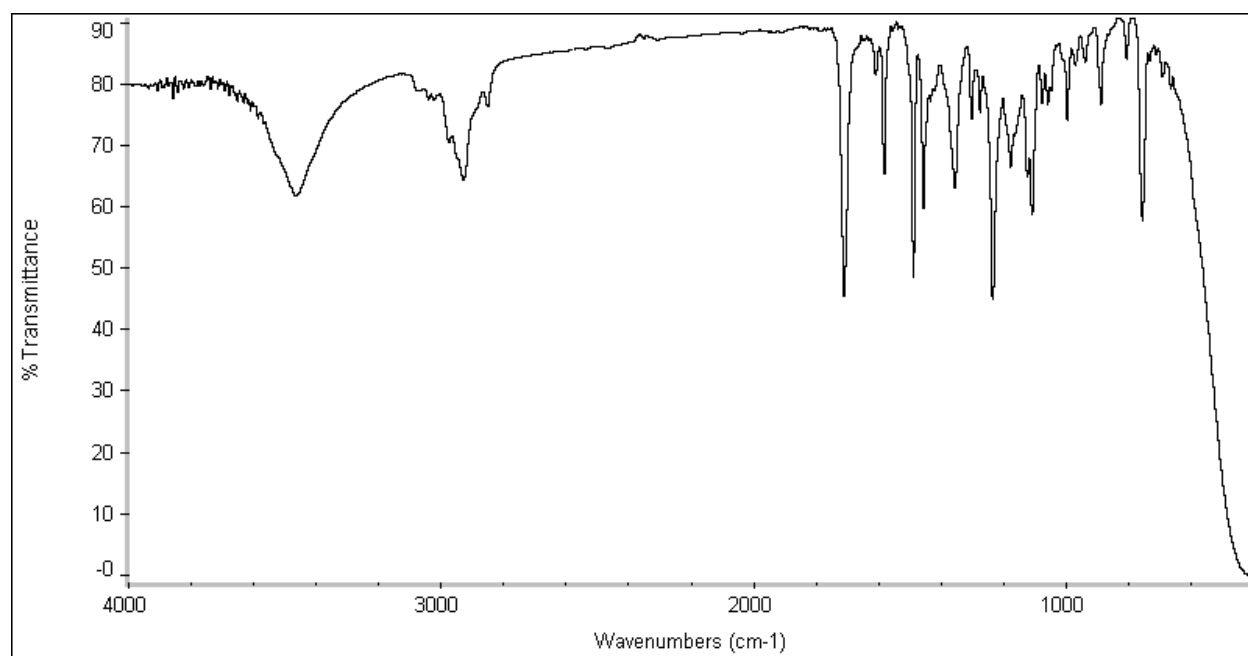
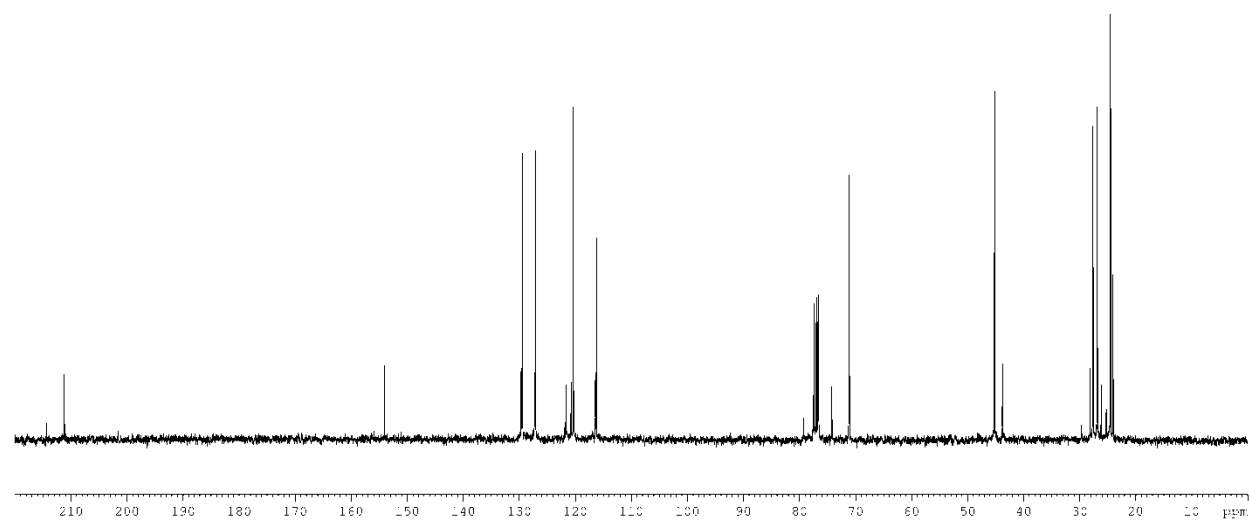
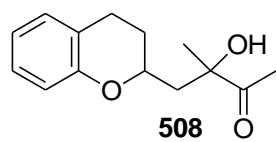


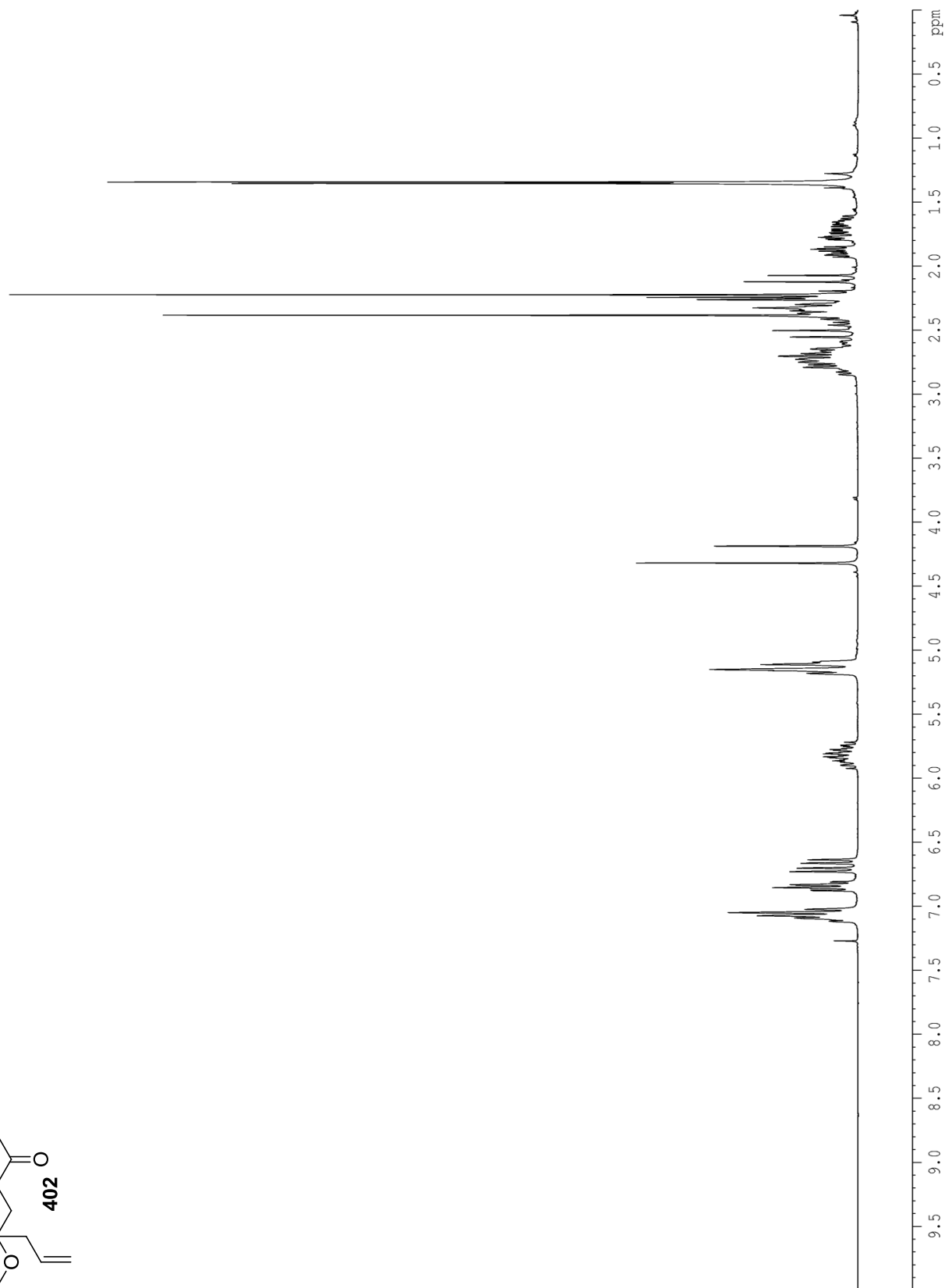
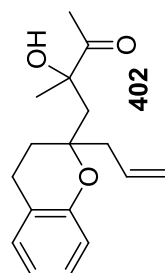


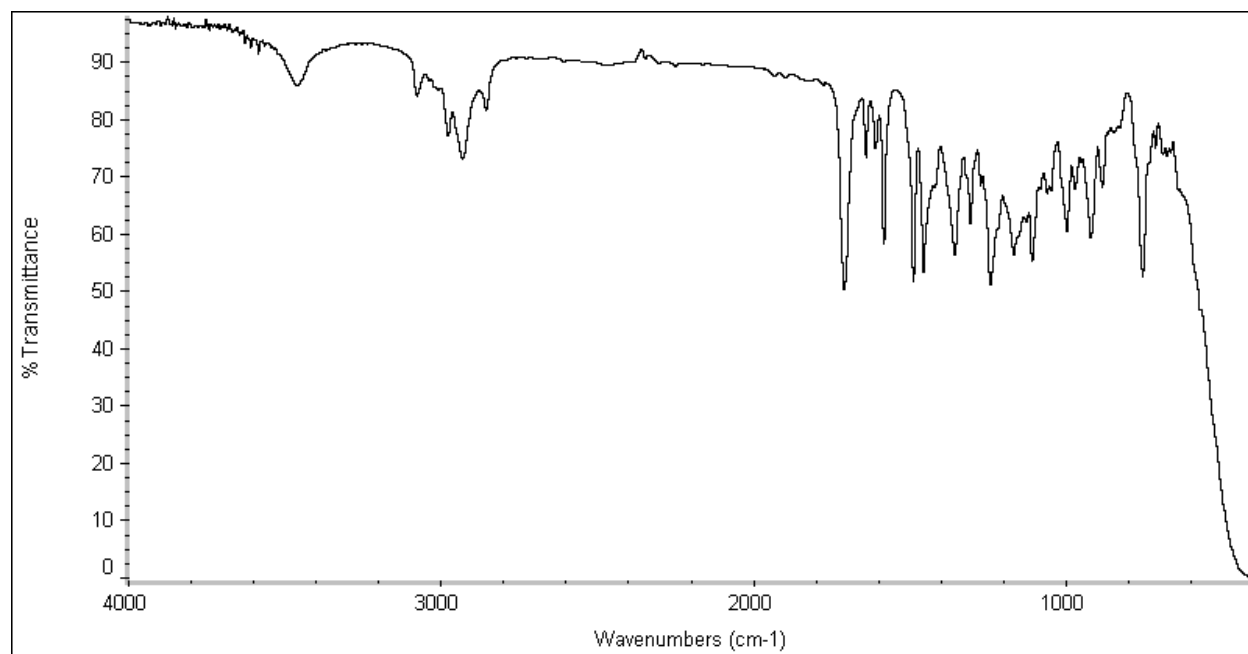
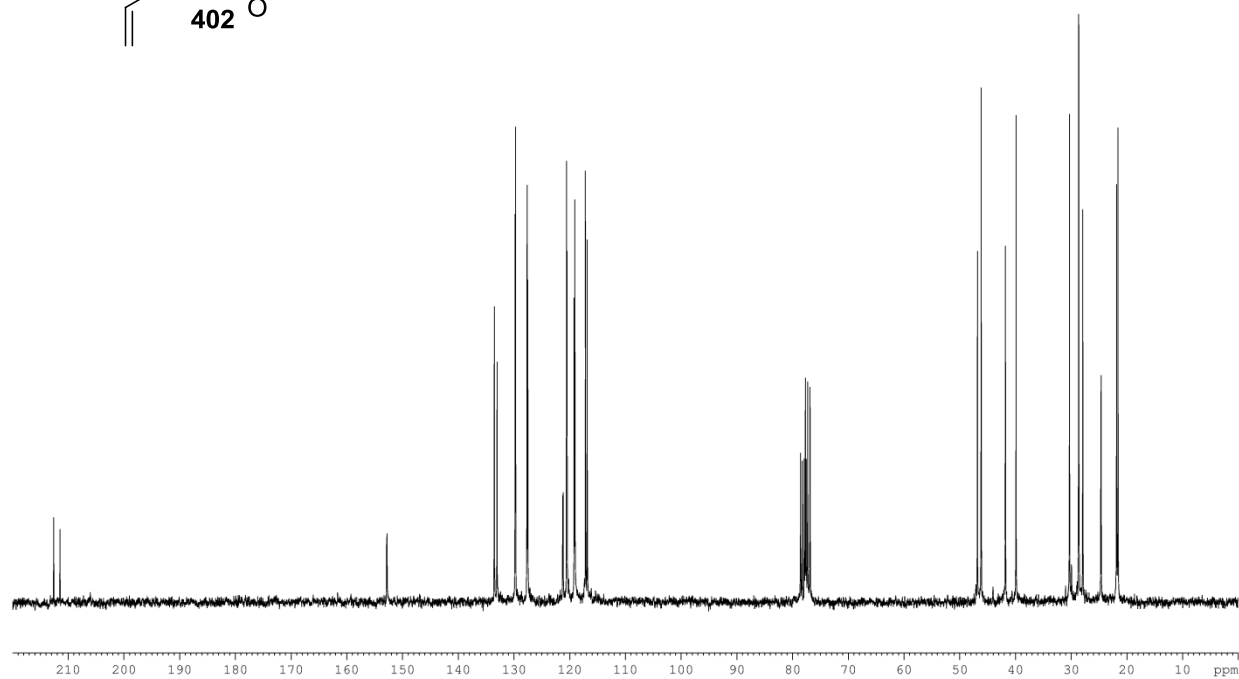
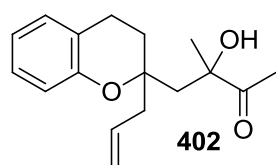


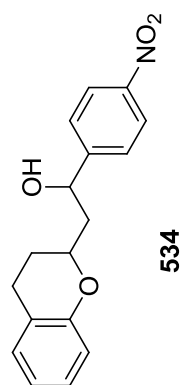




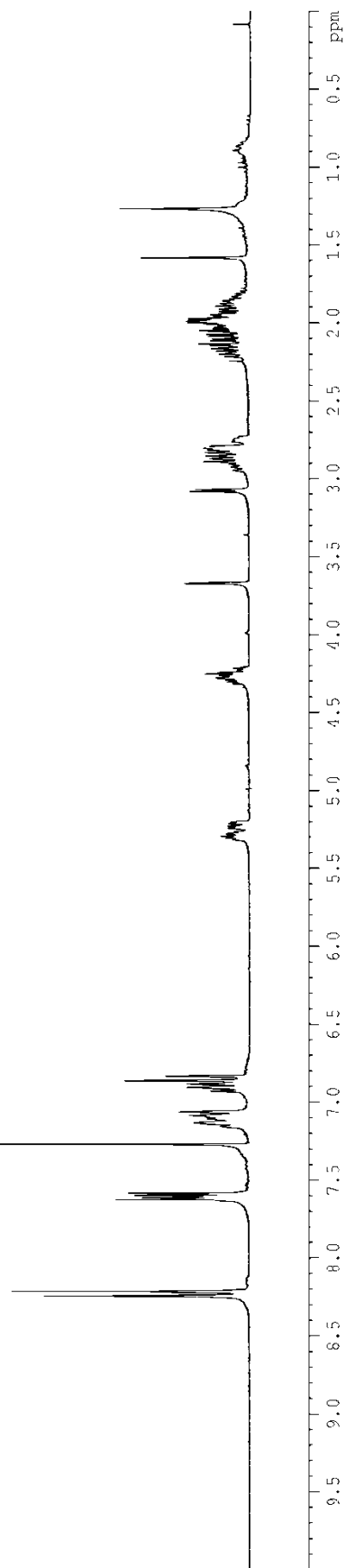


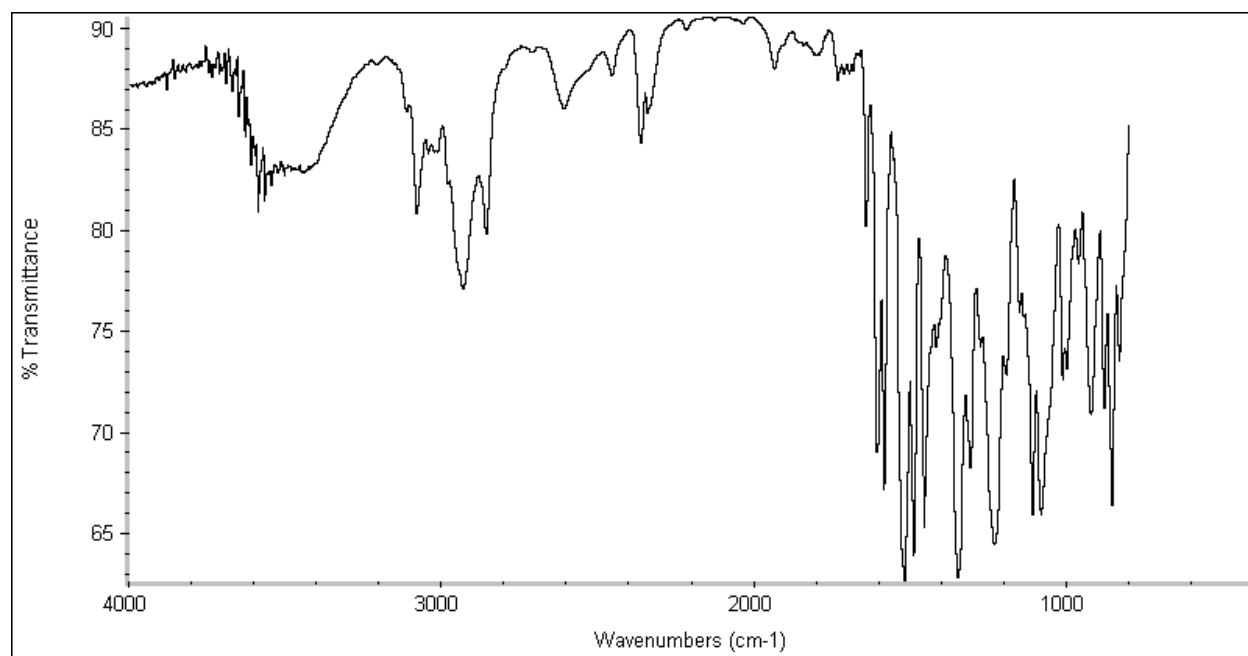
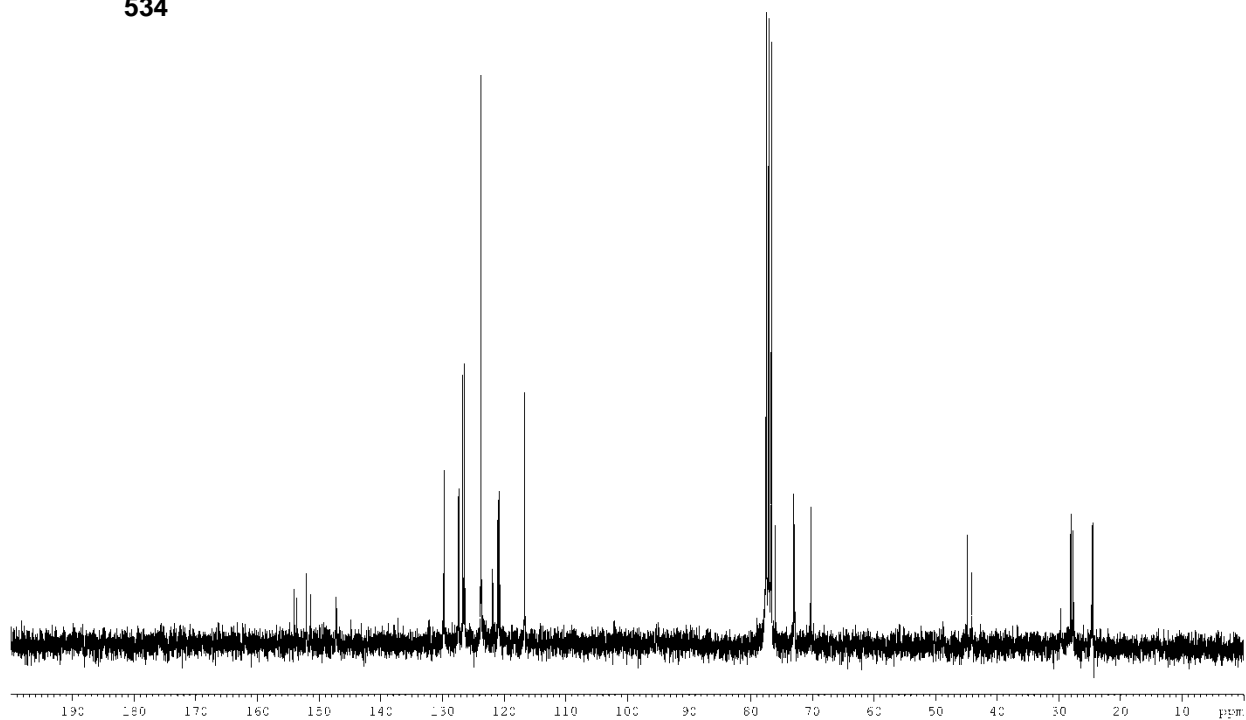
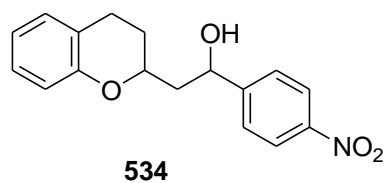


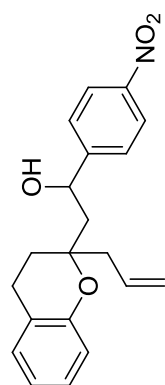




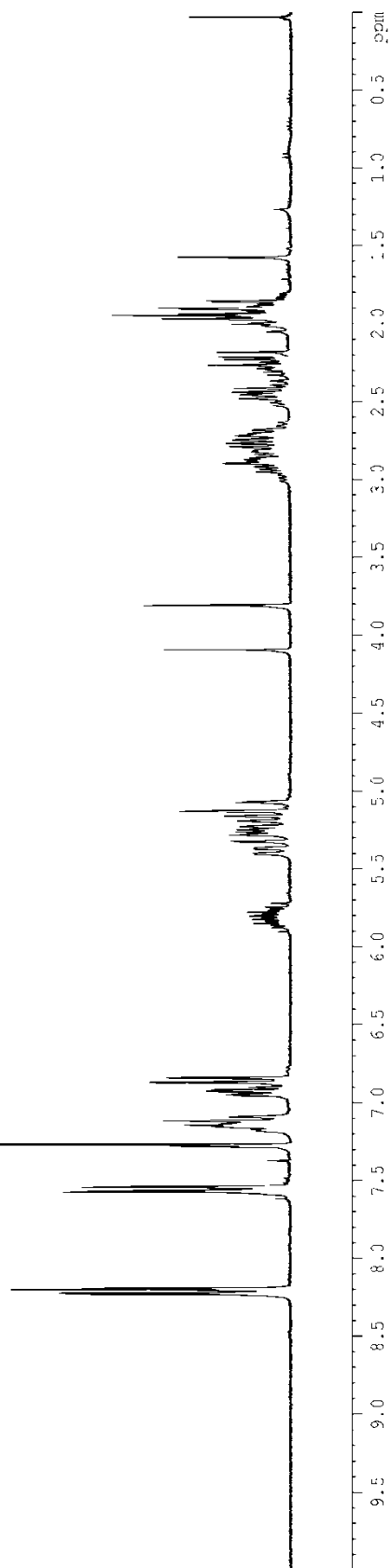
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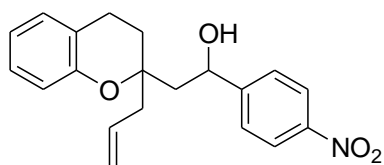




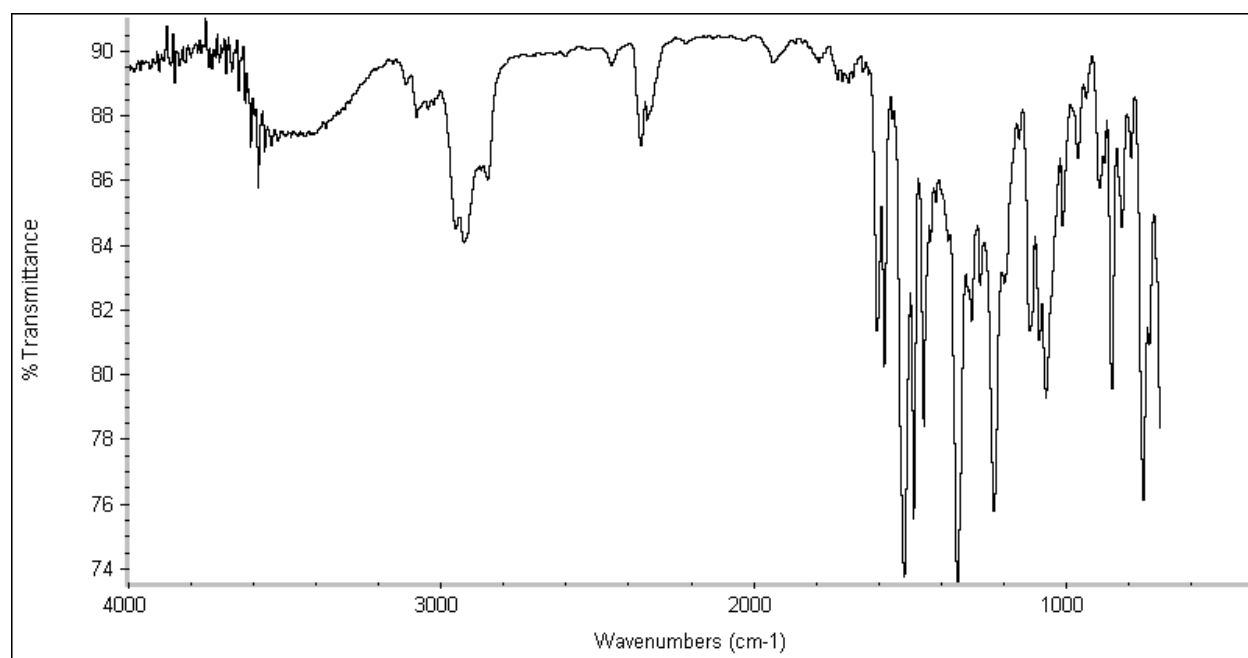
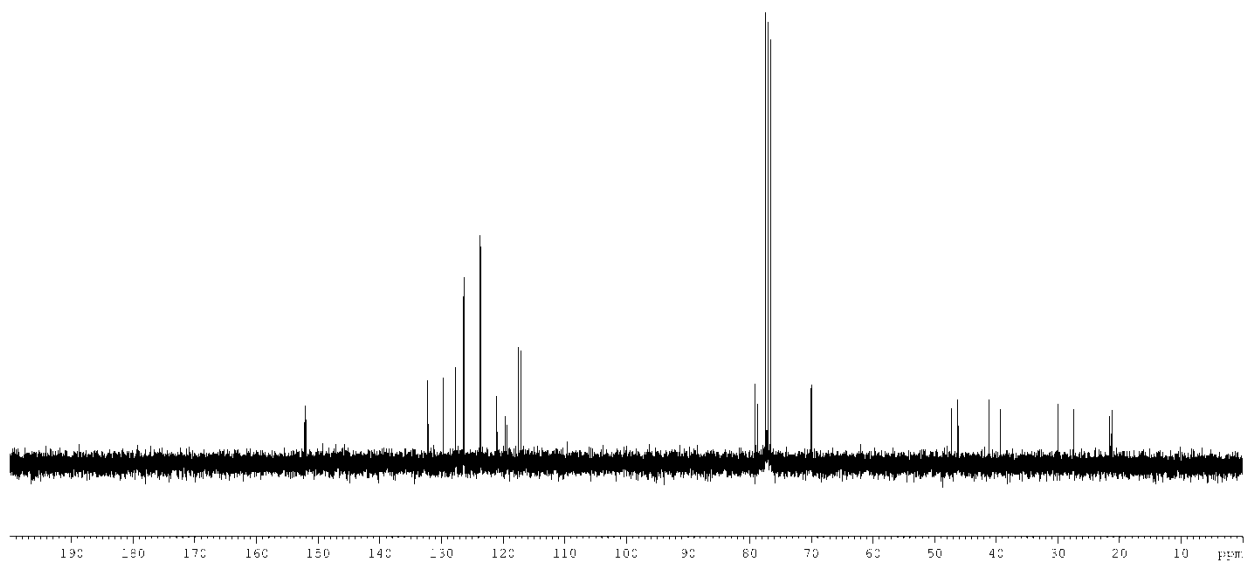


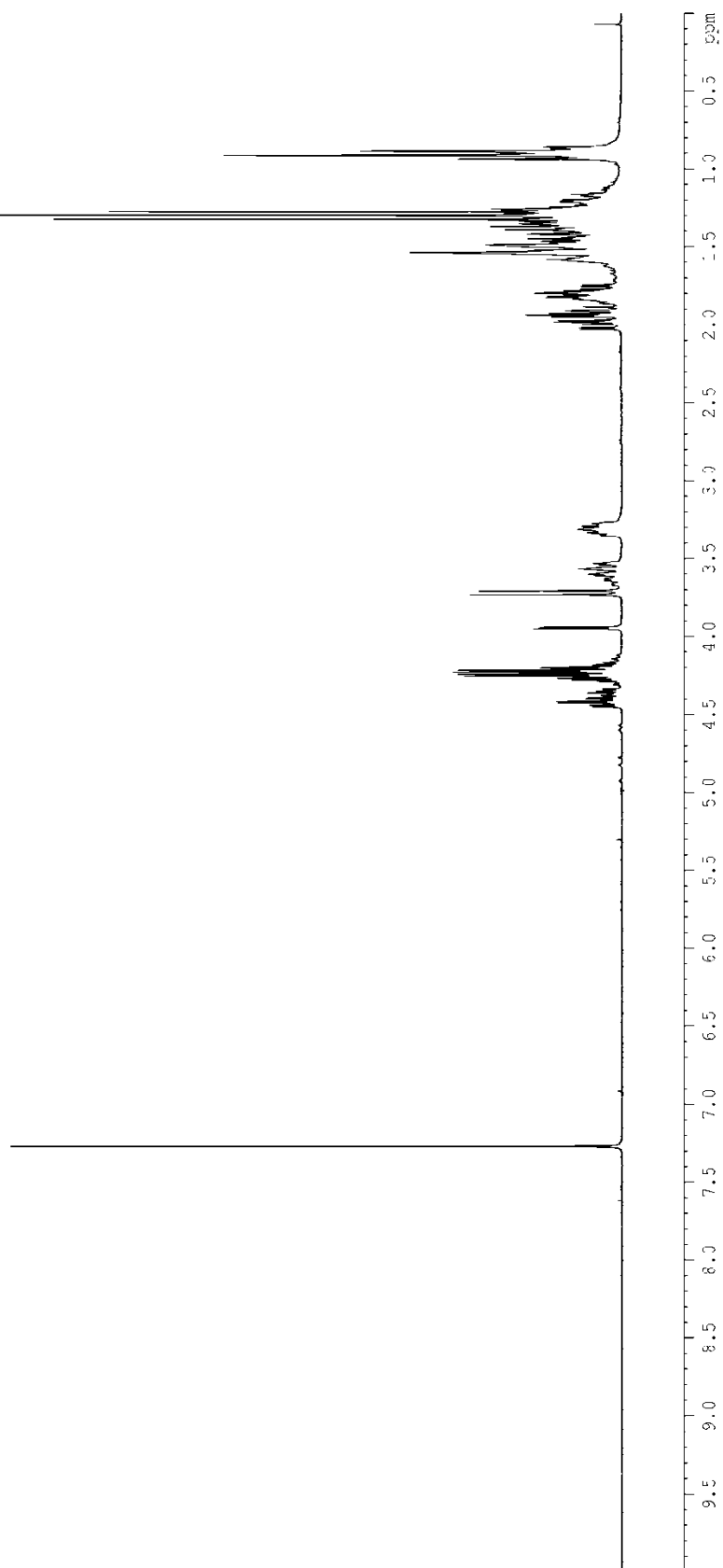
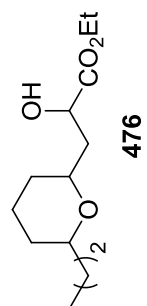
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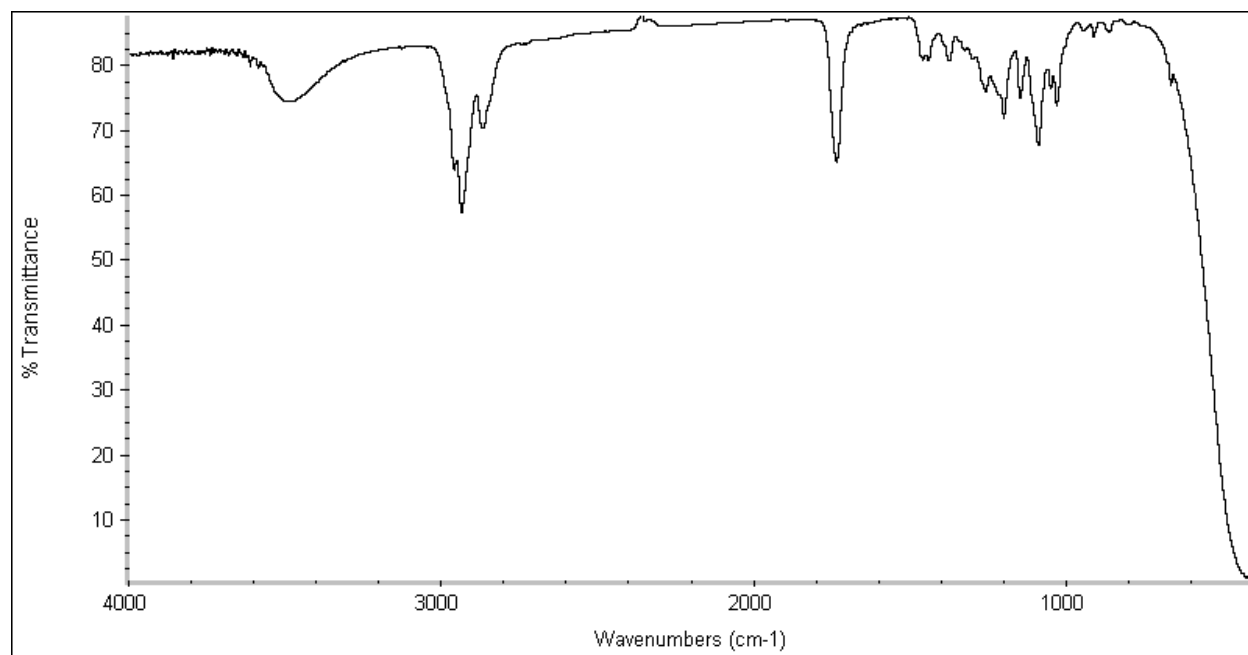
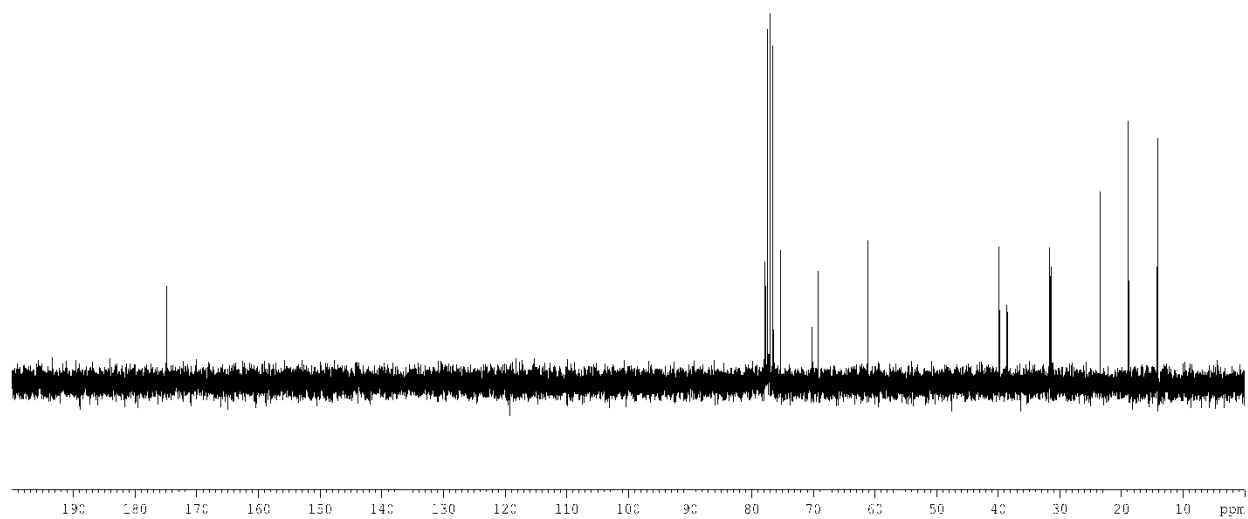
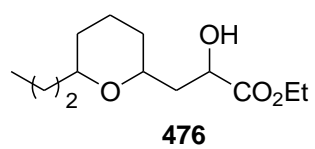




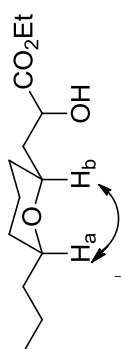
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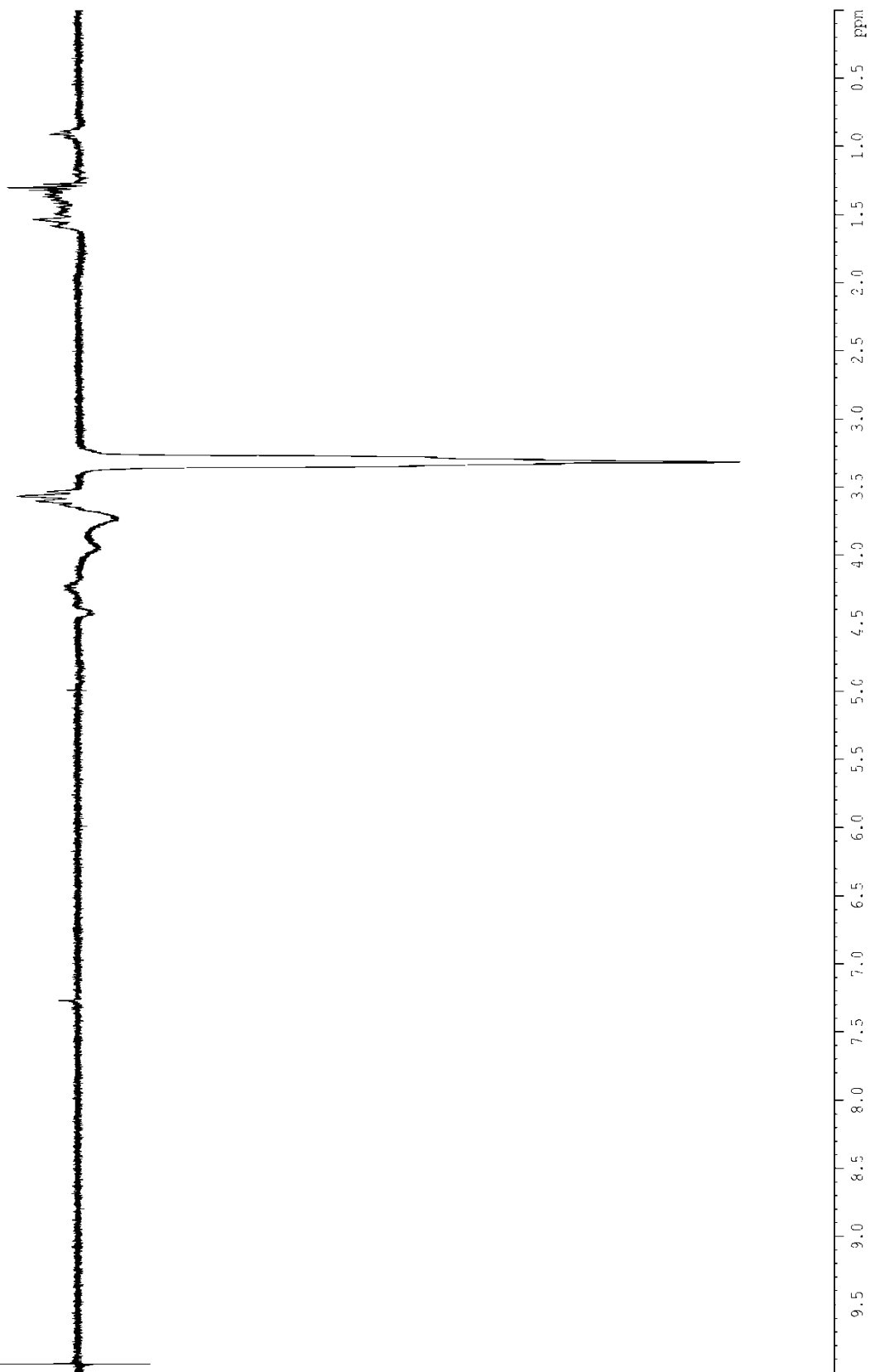


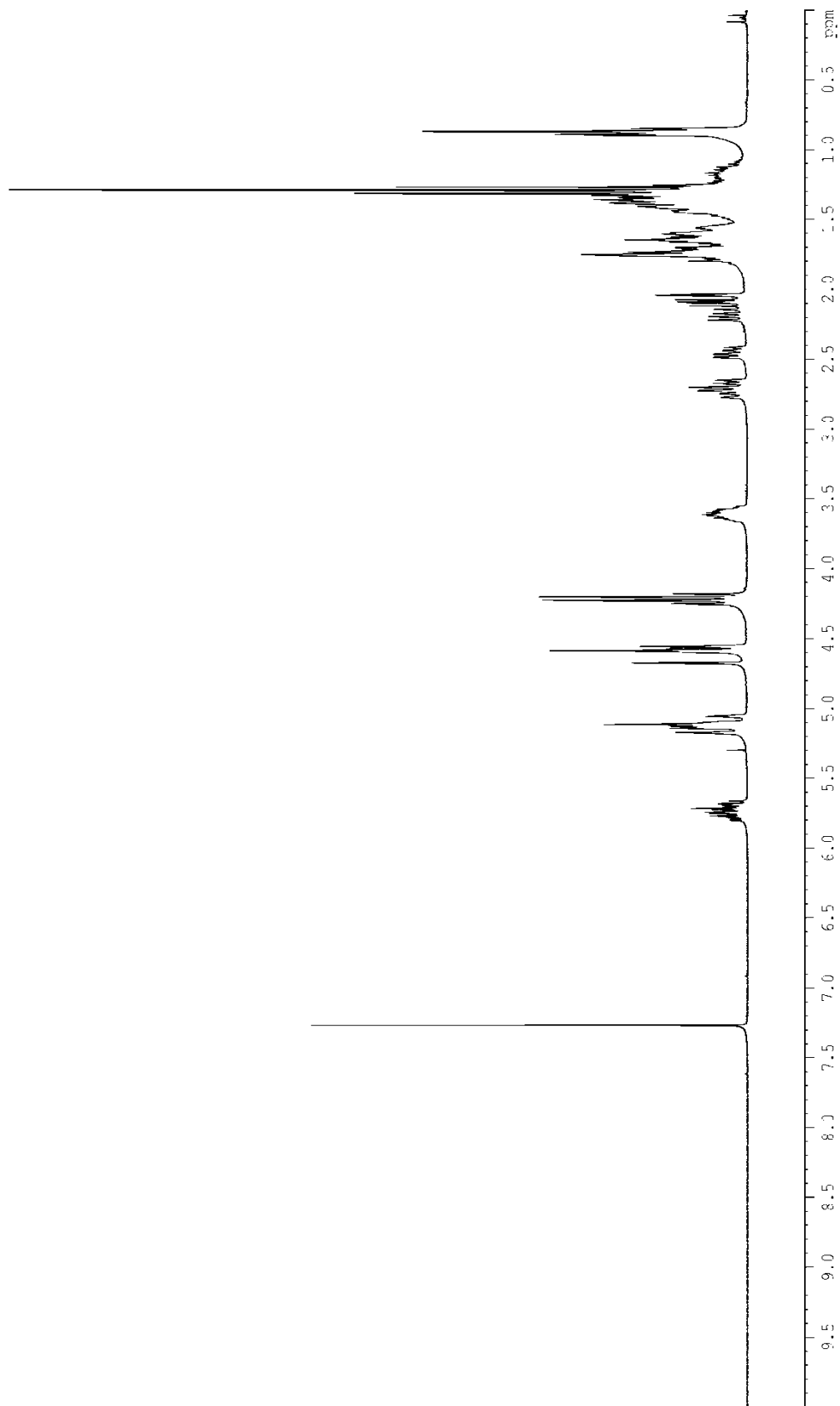


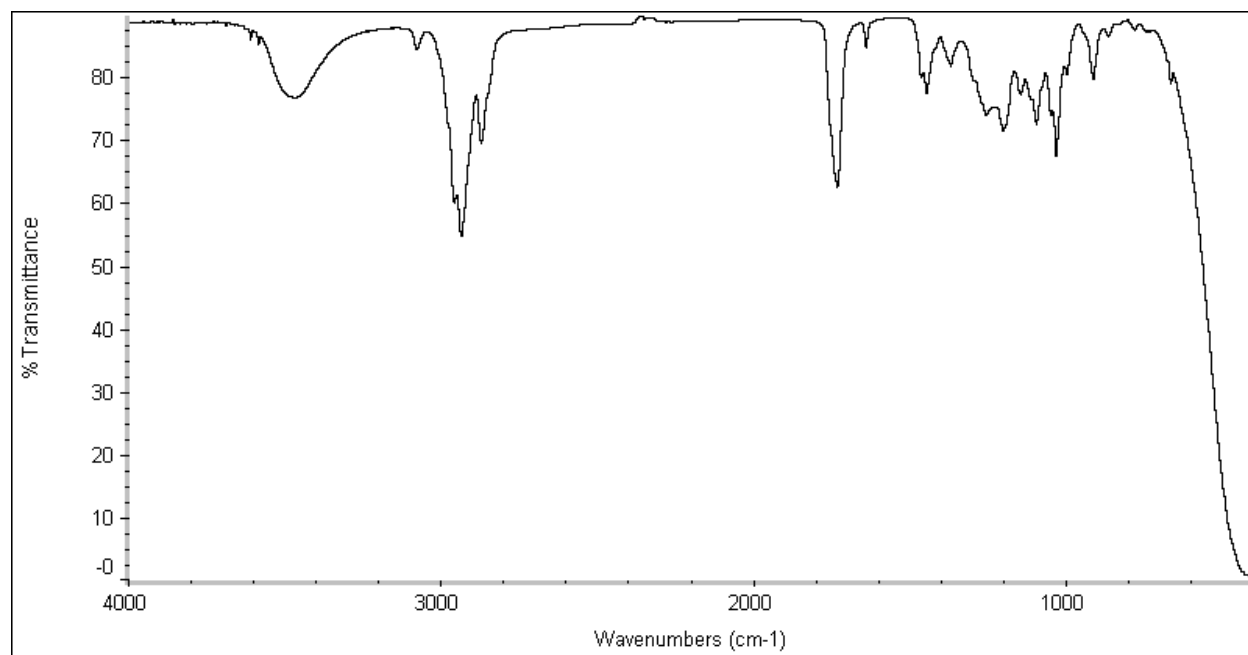
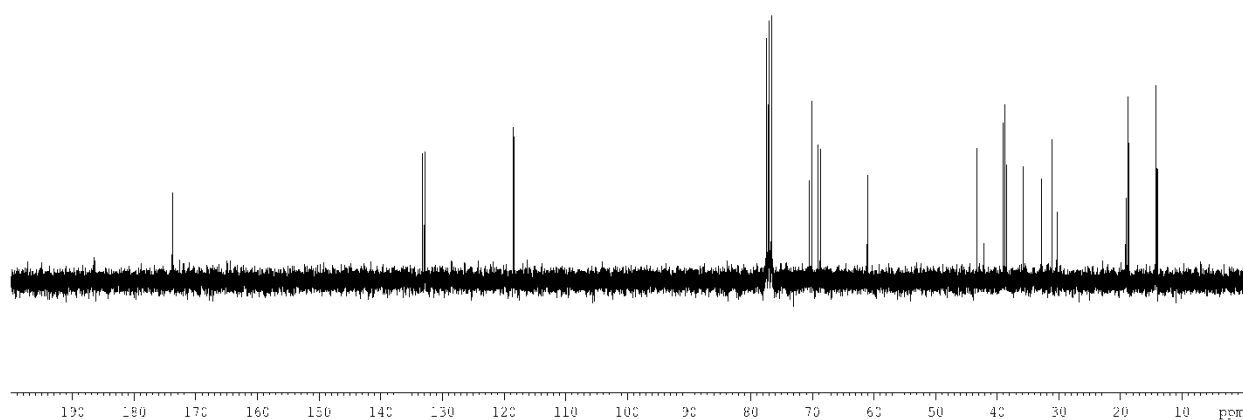
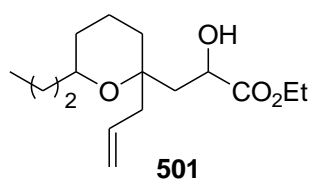
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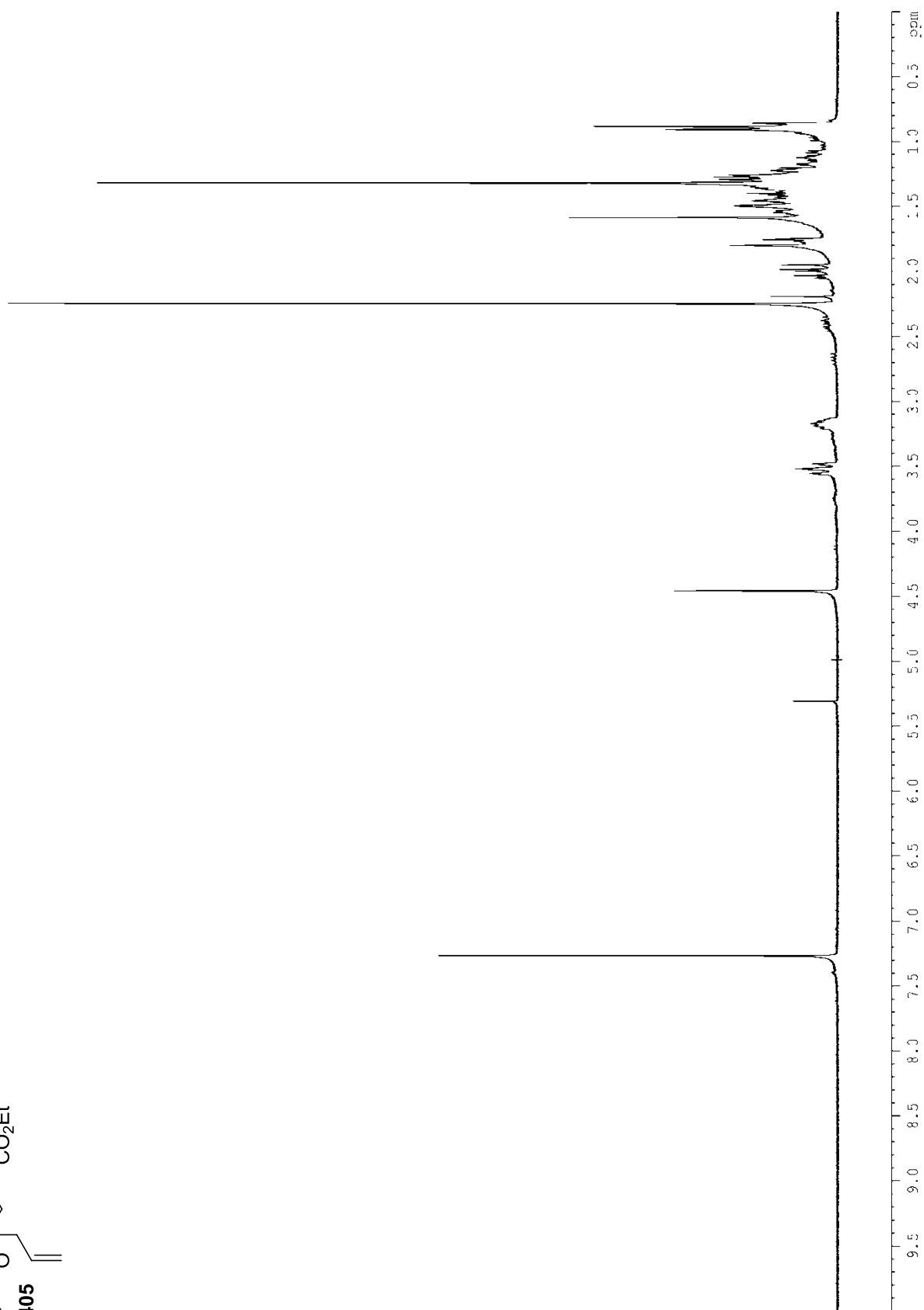
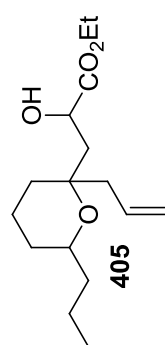


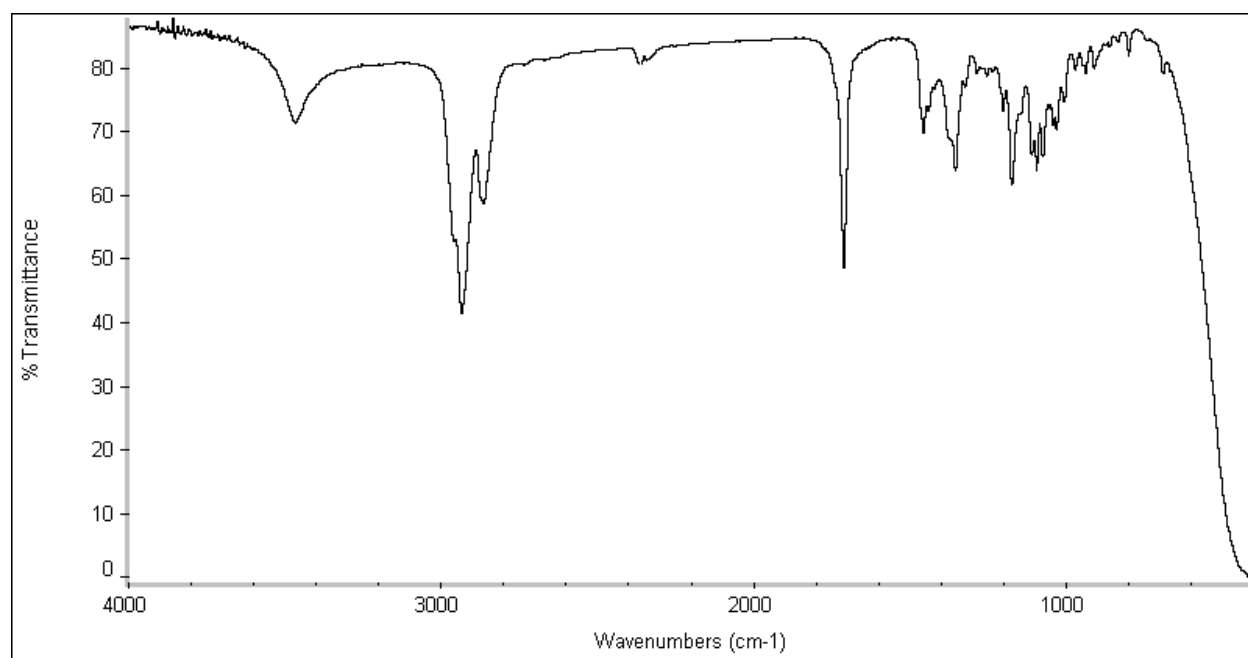
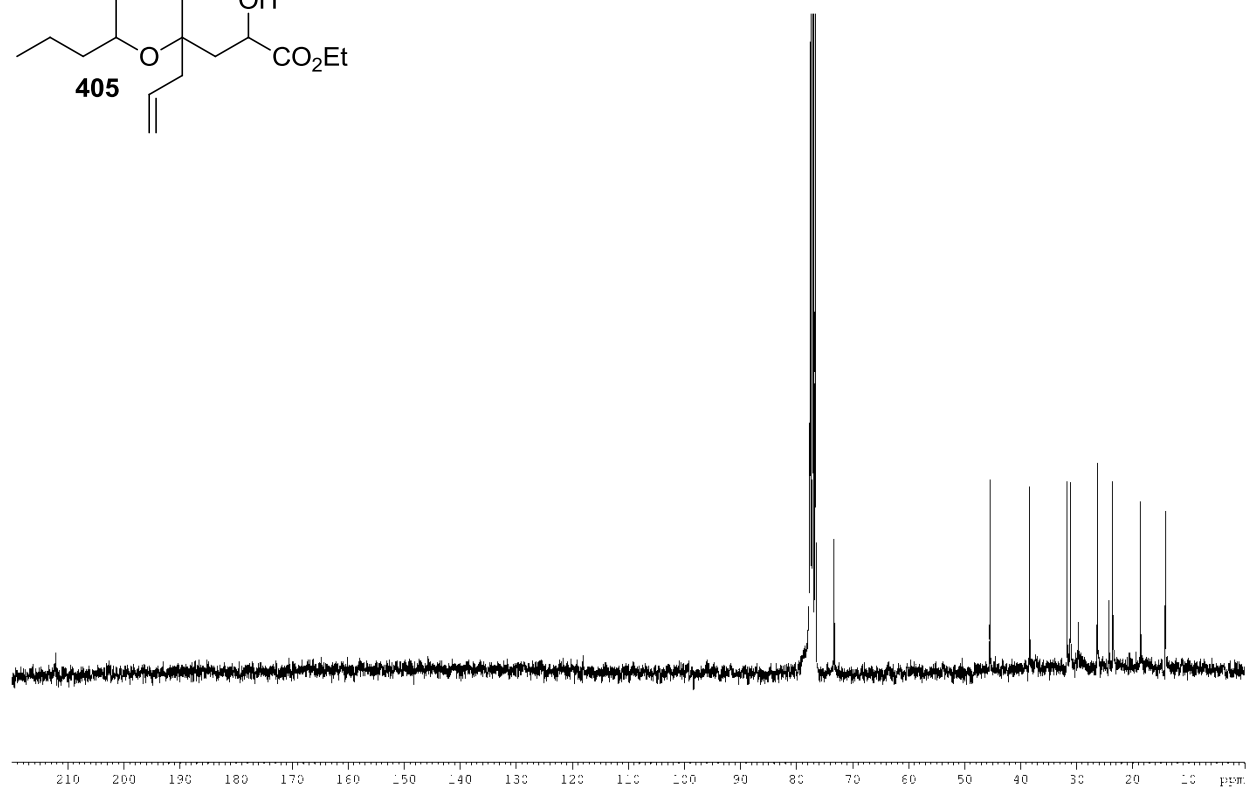
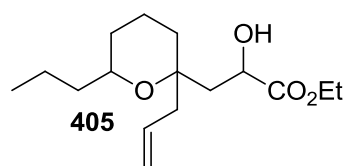
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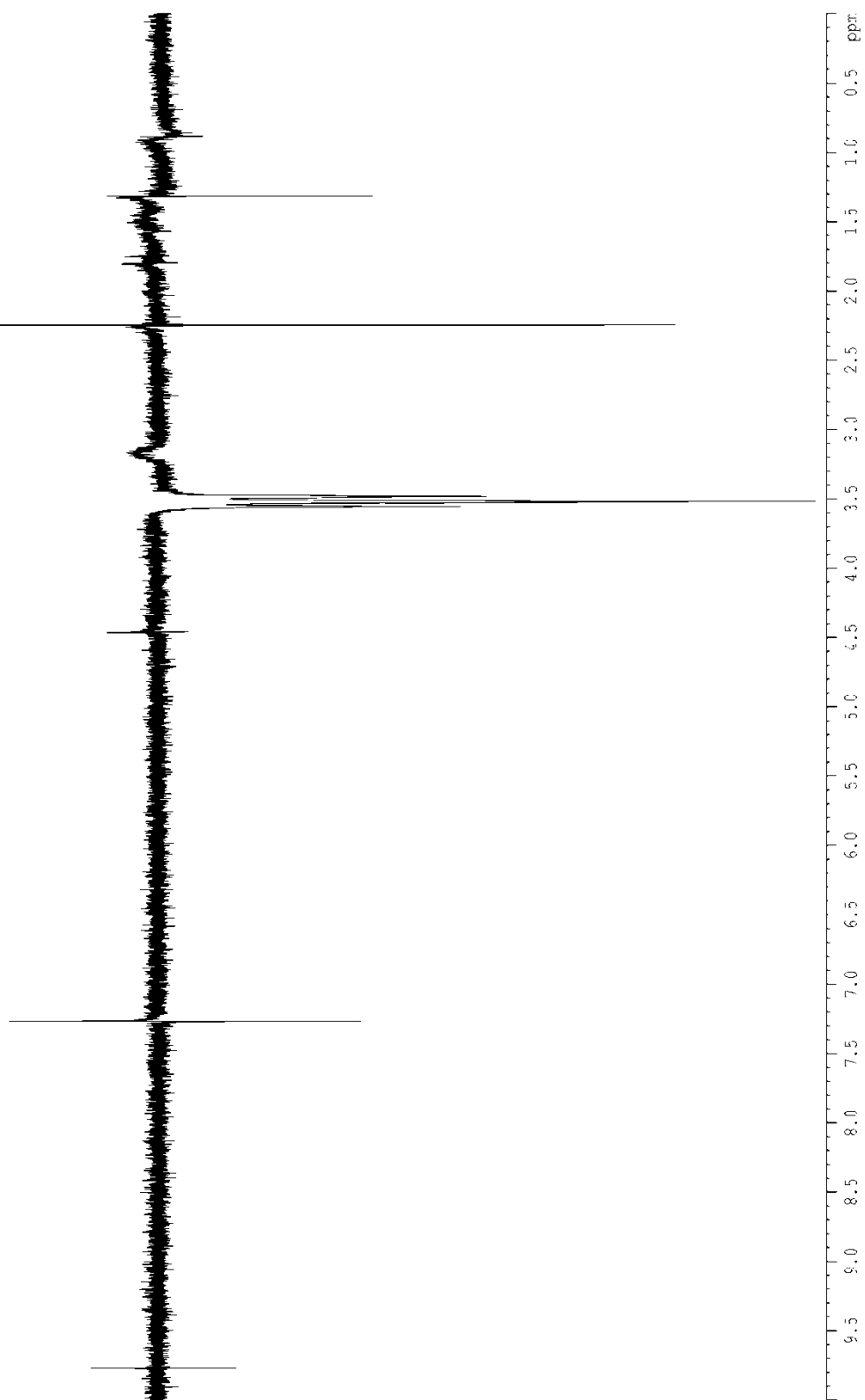
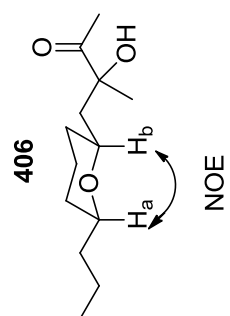


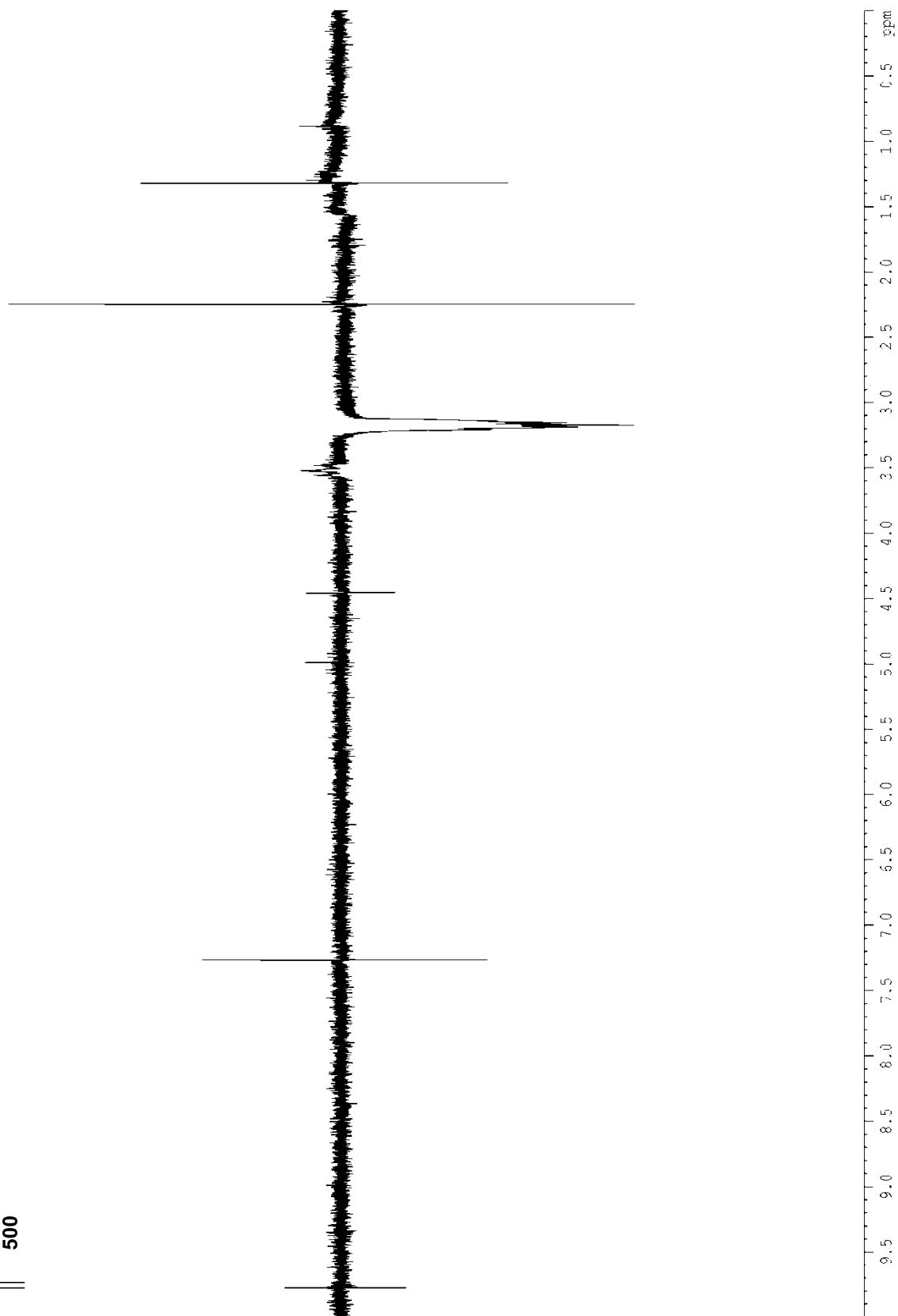
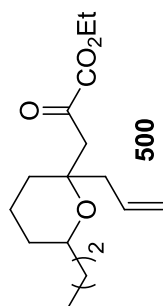


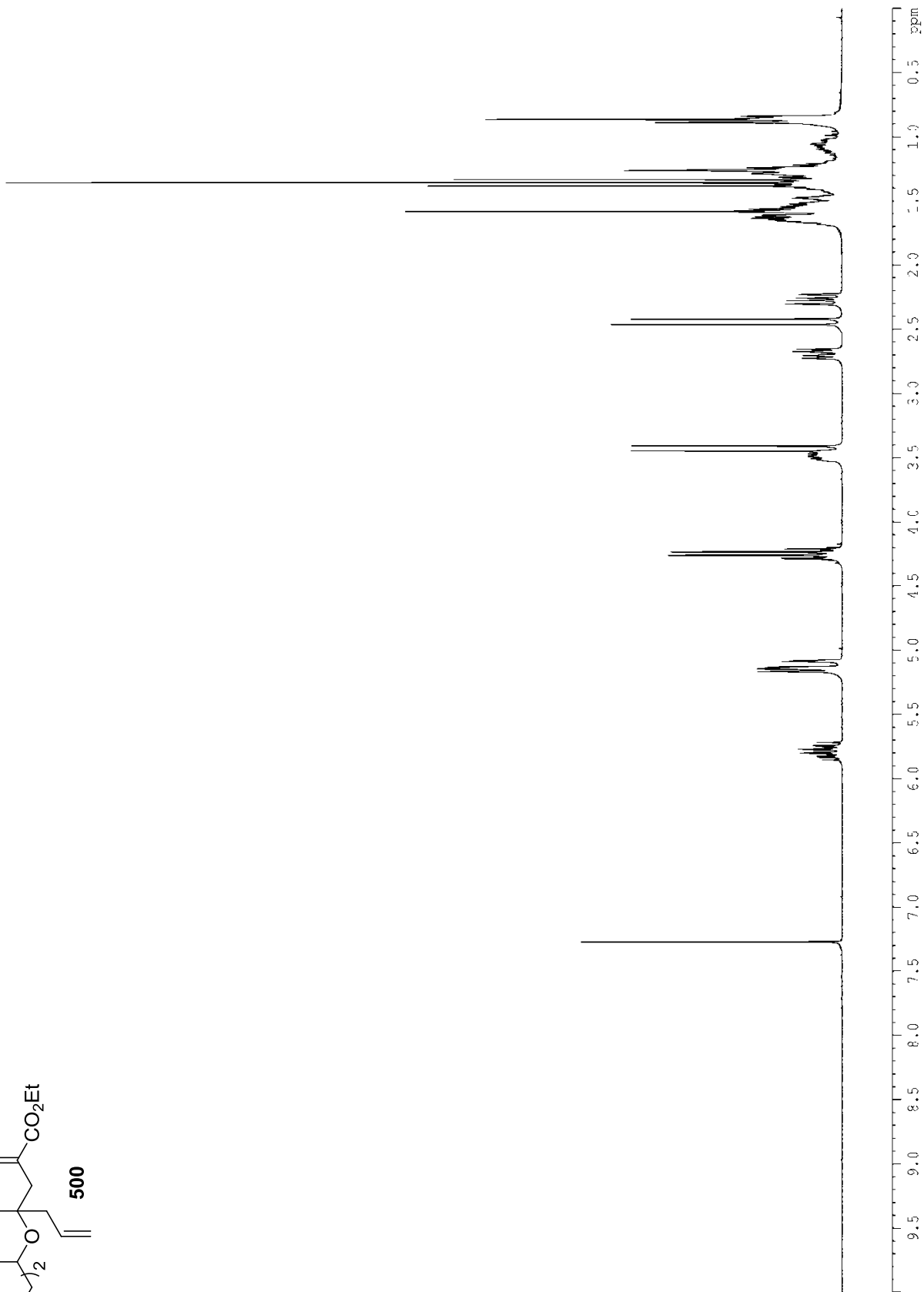


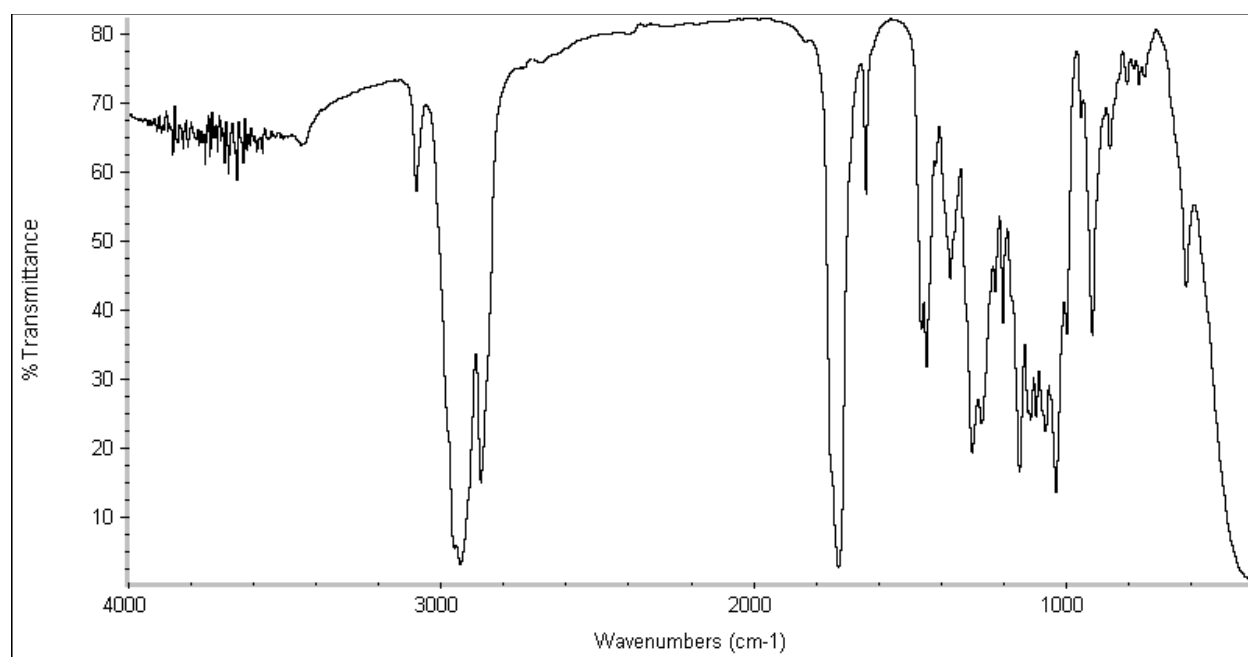
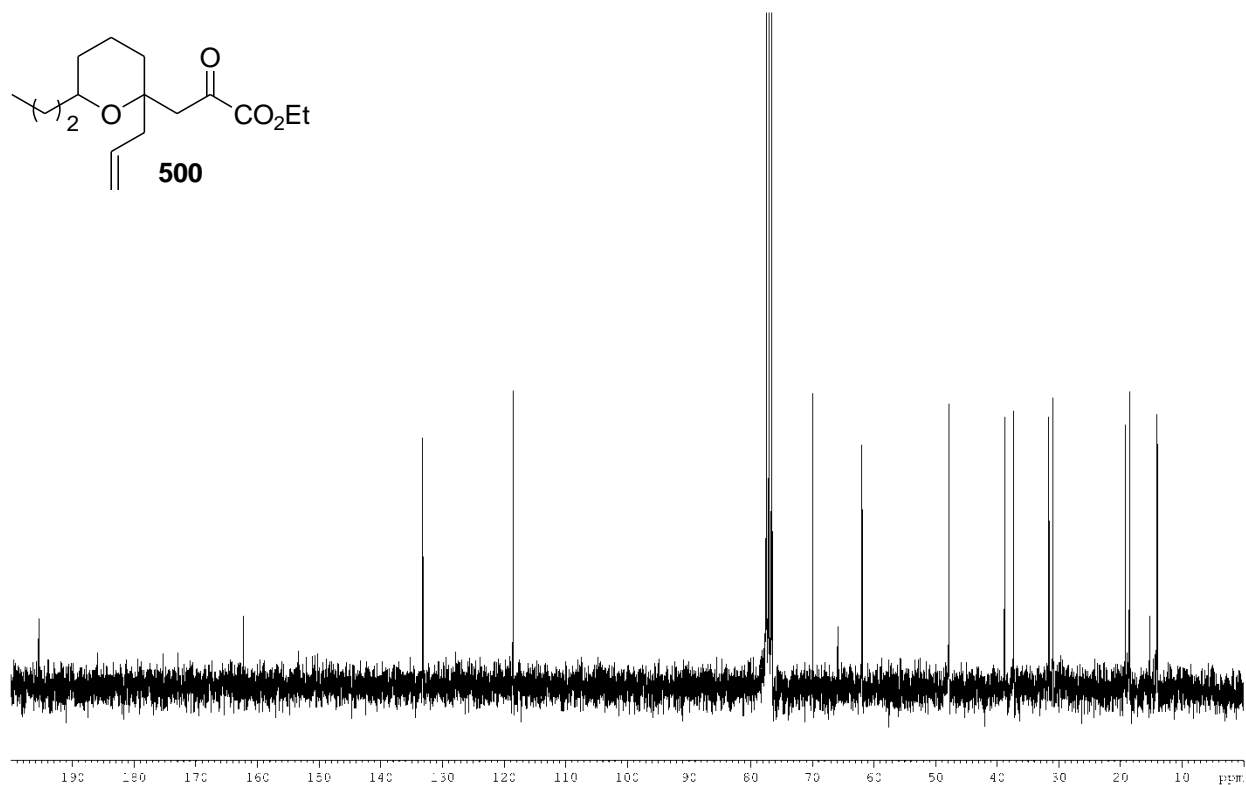


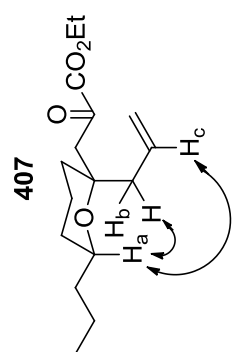




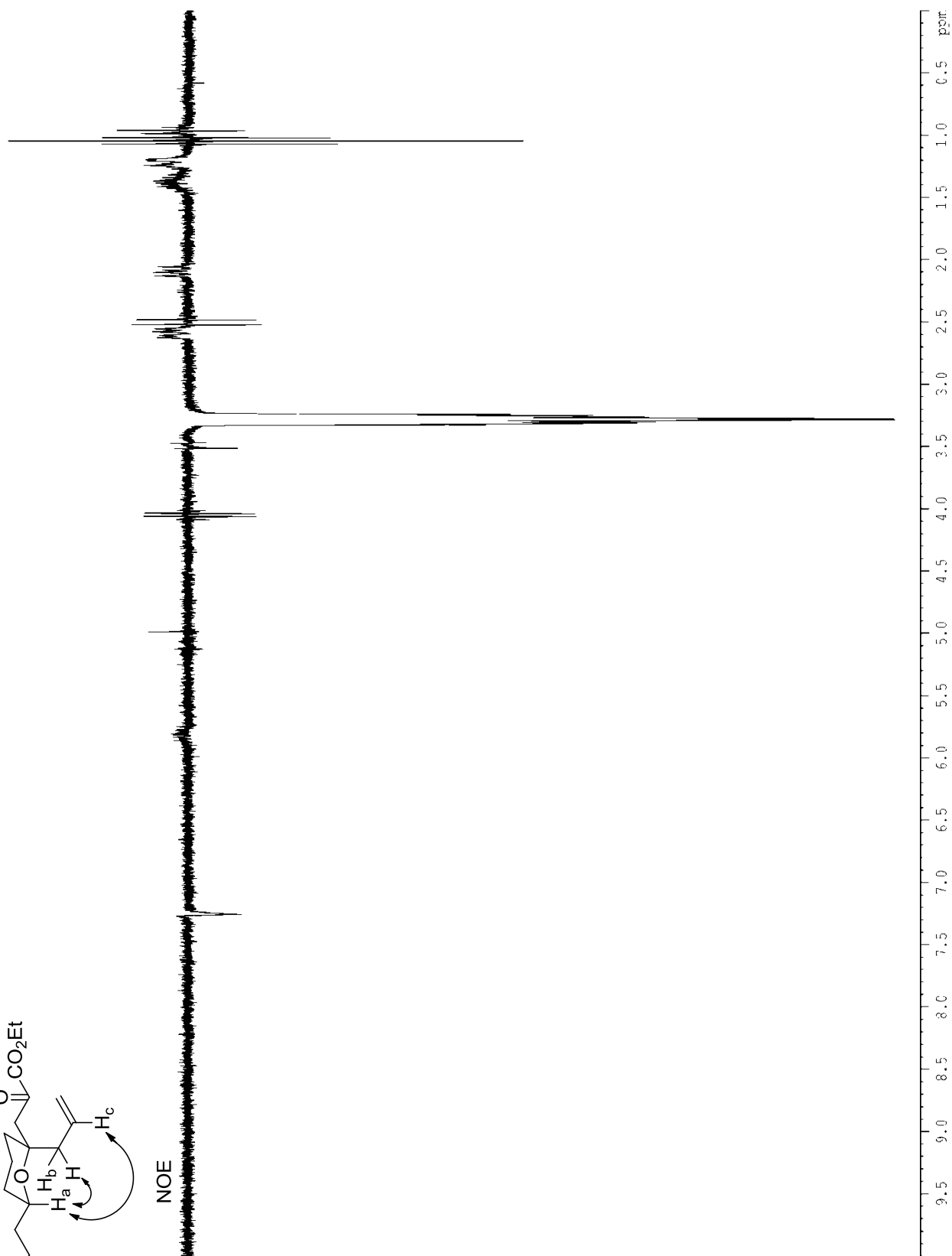






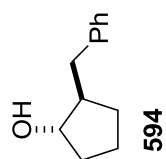


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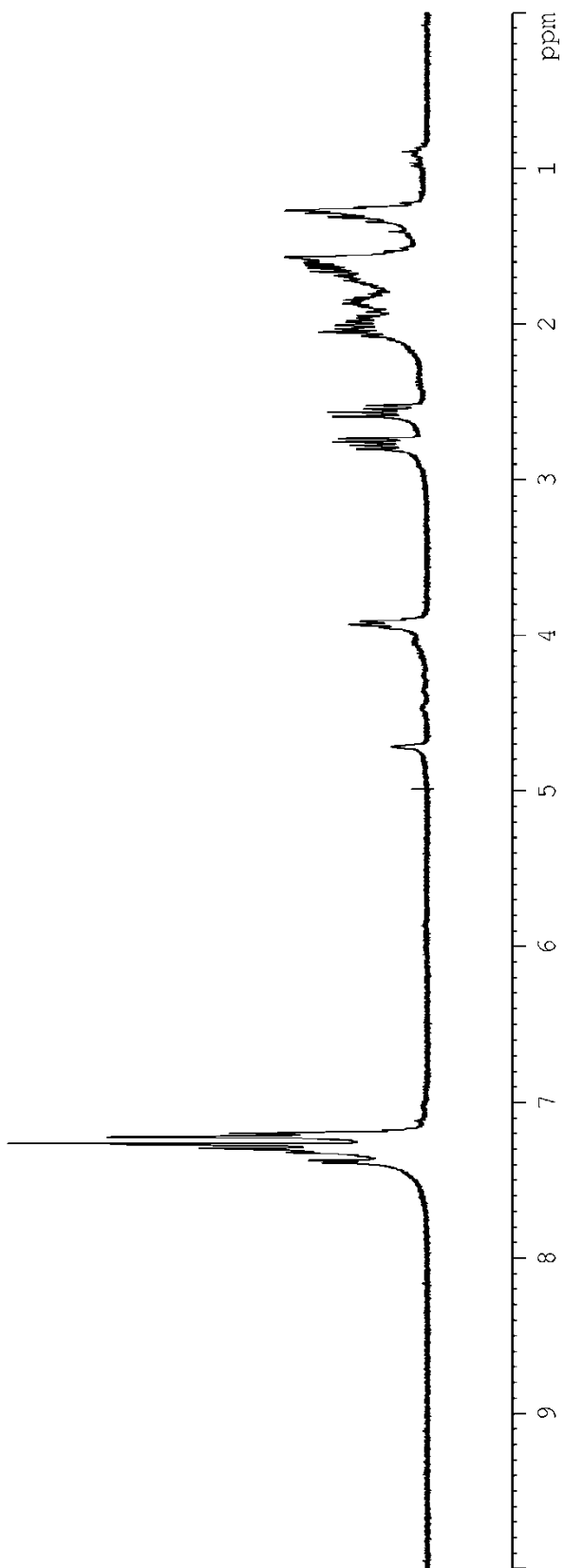


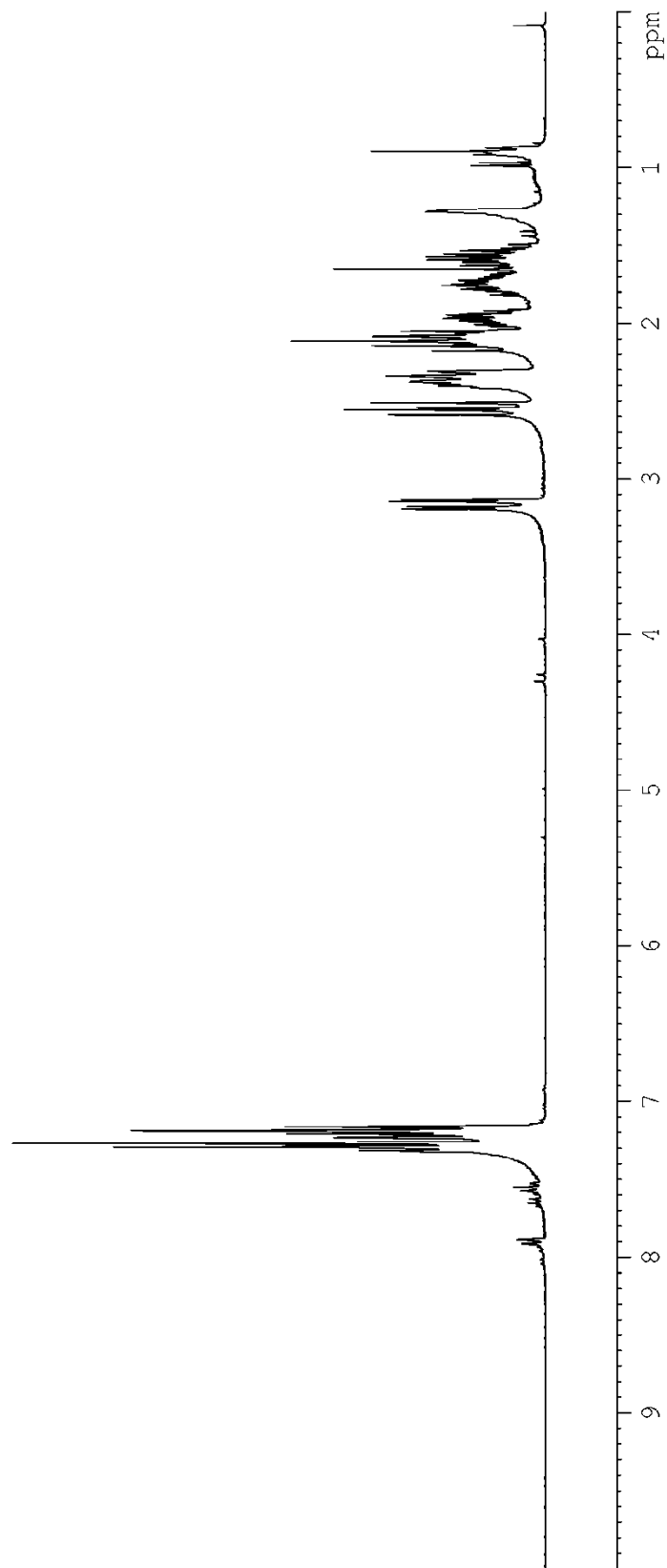
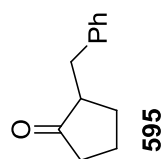
Appendix 2

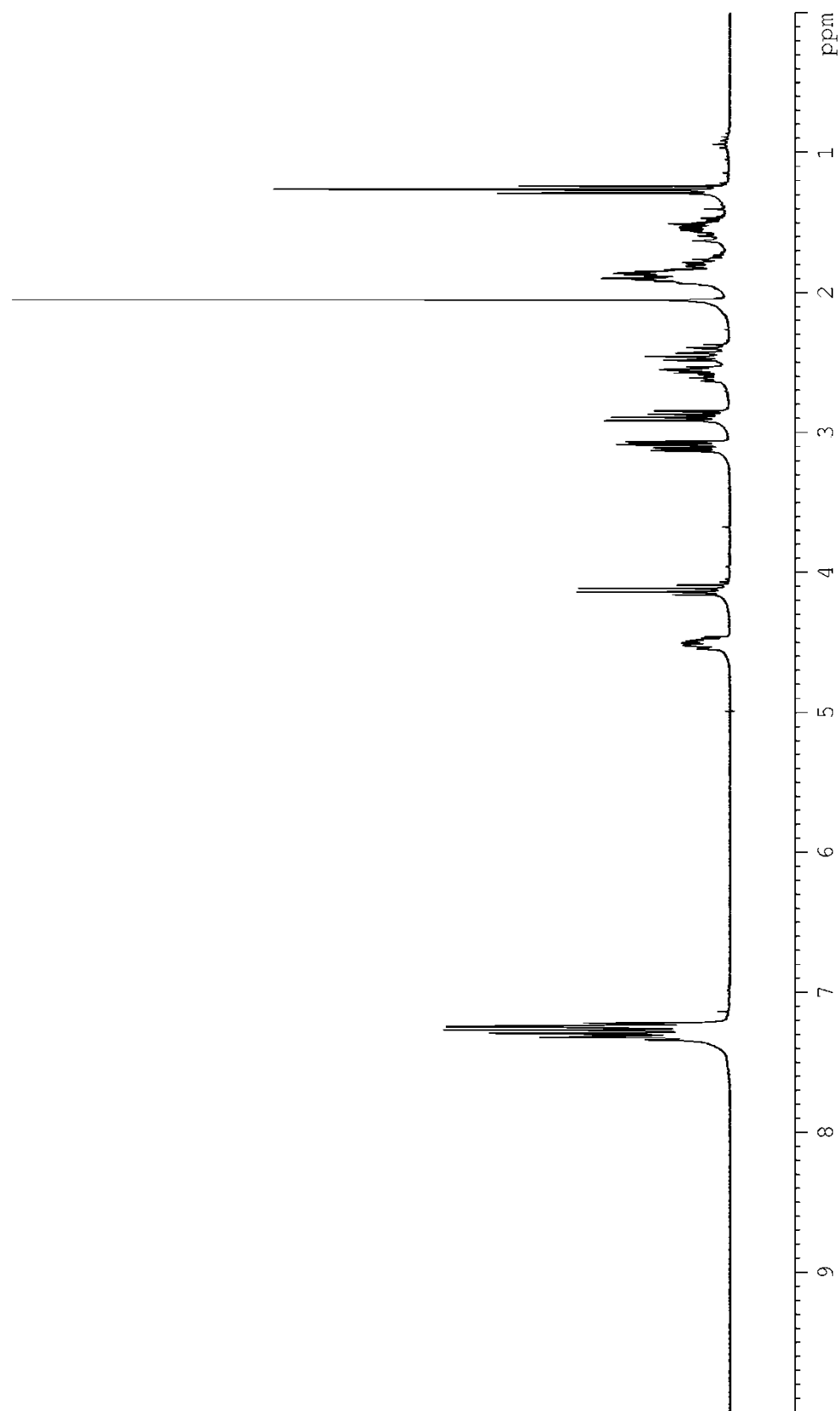
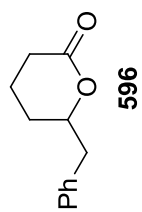
Selected Spectral Data for Chapter 3: Carbonyl-Ene Reactions of Substituted Exocyclic Enol Ethers

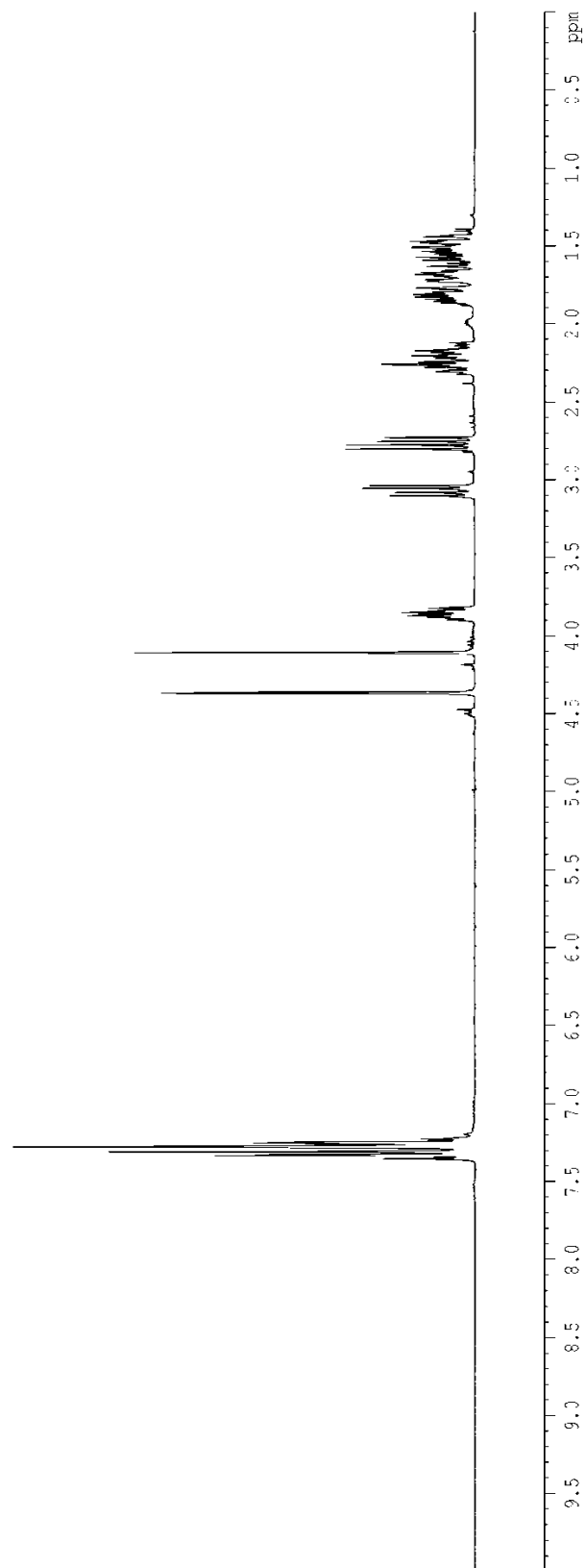
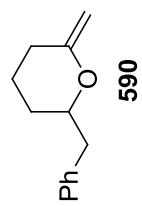


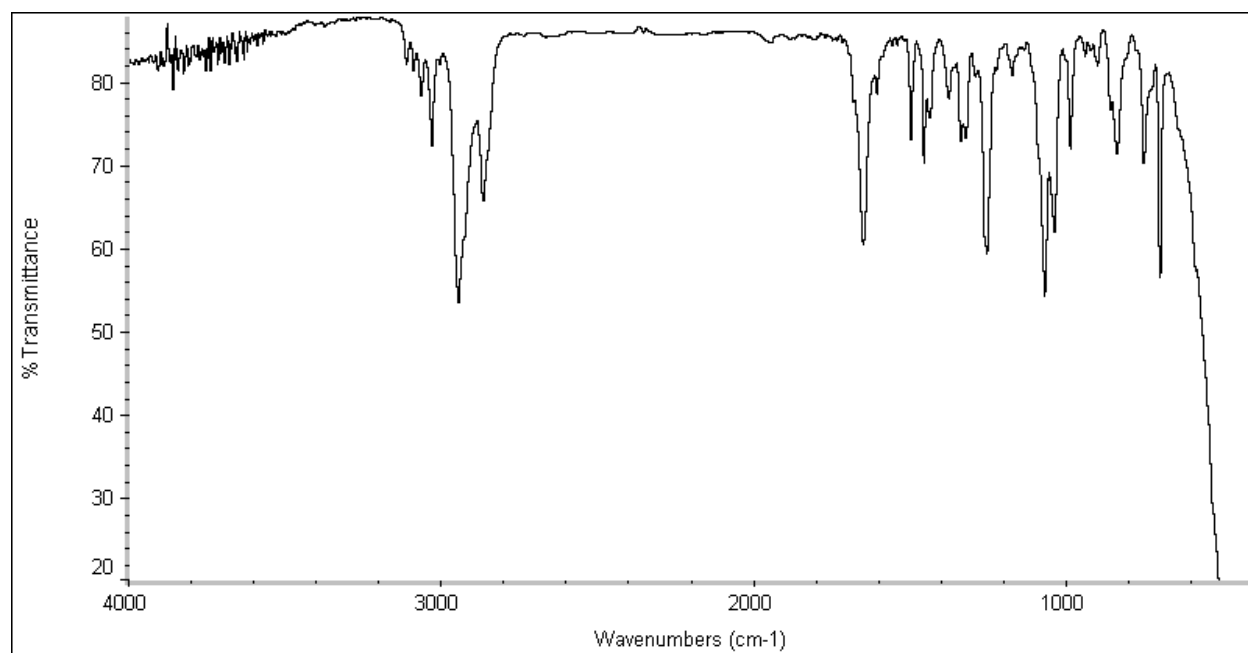
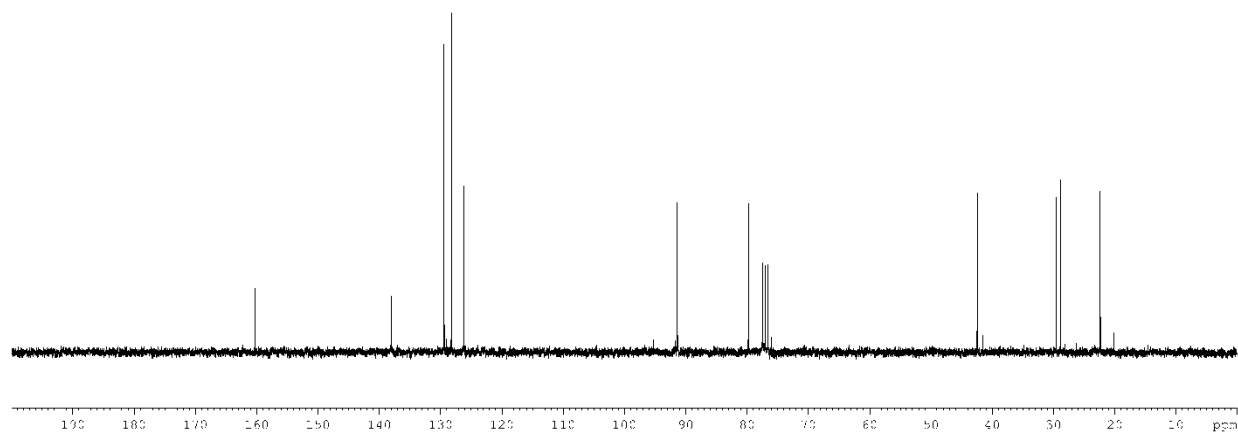
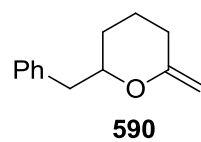
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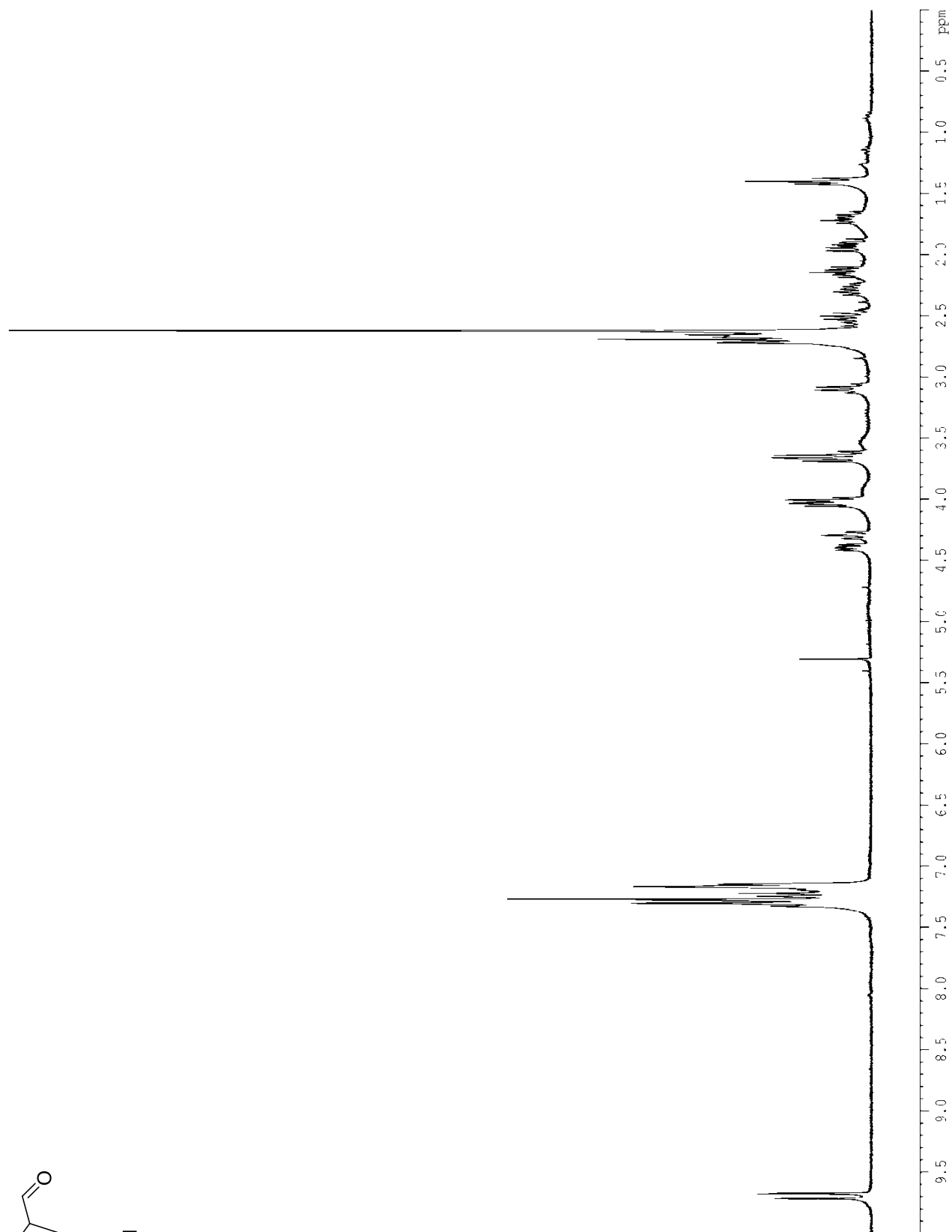
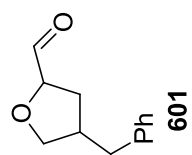


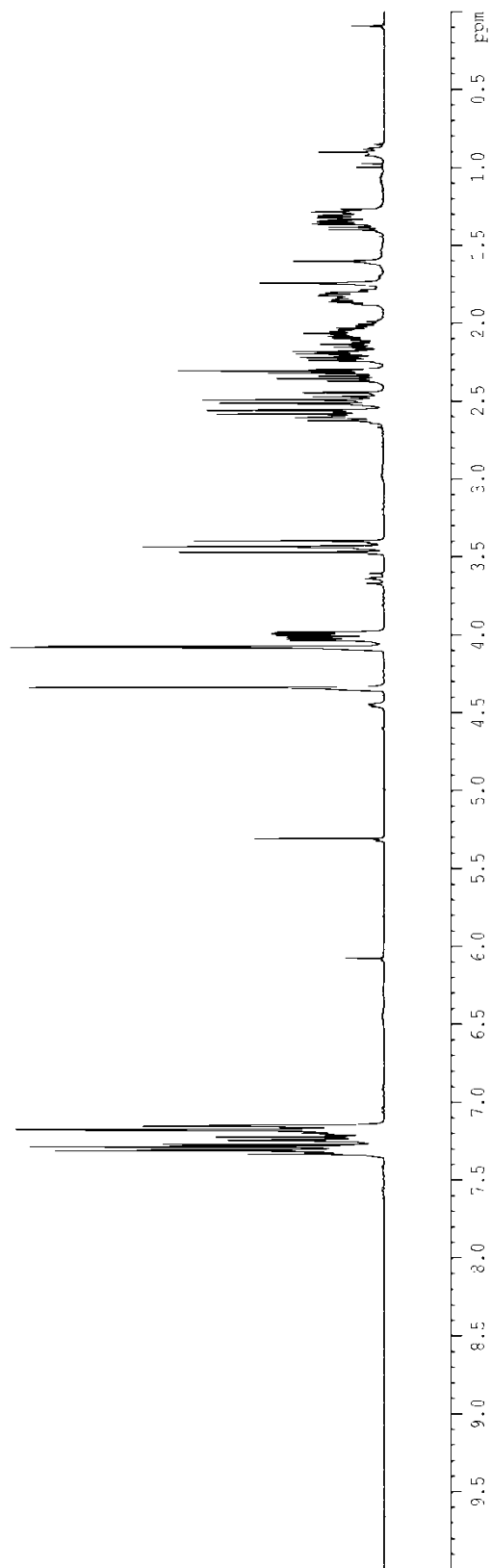
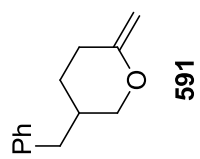


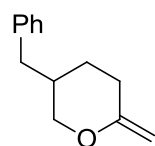




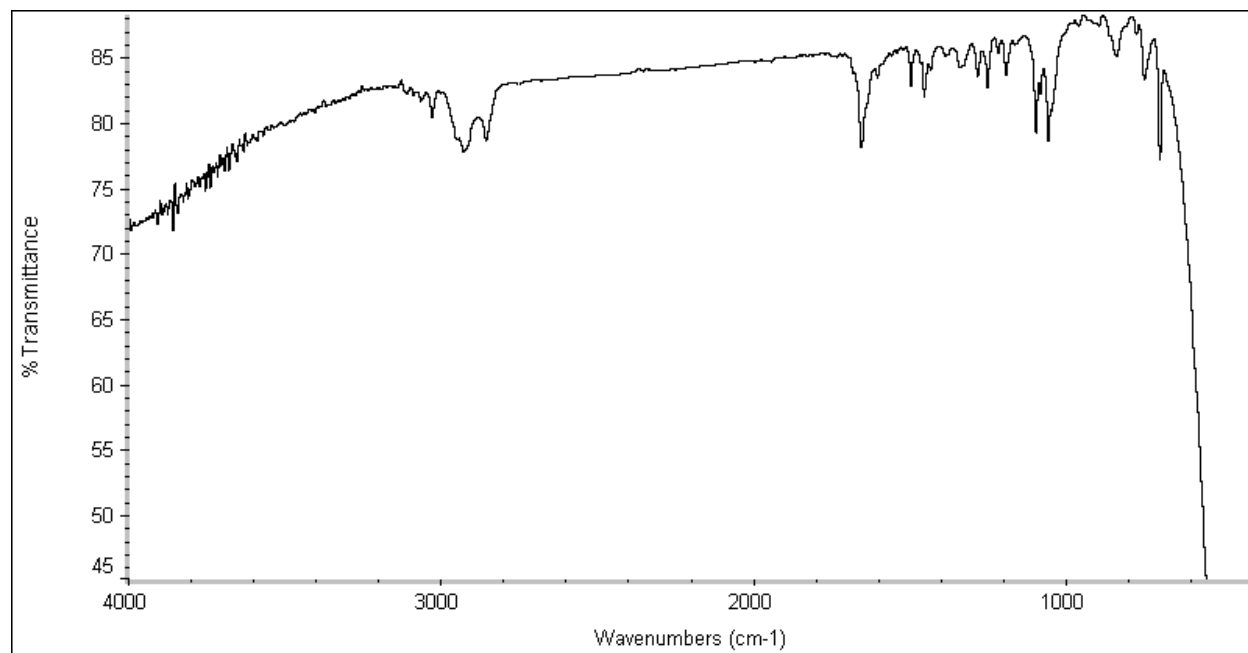
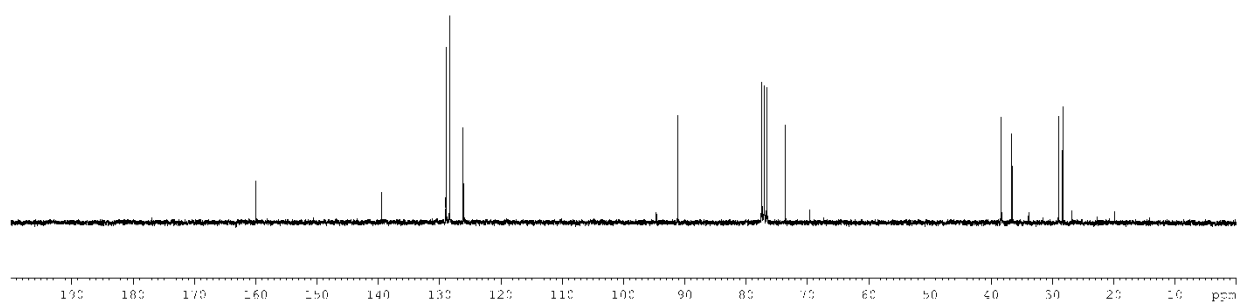


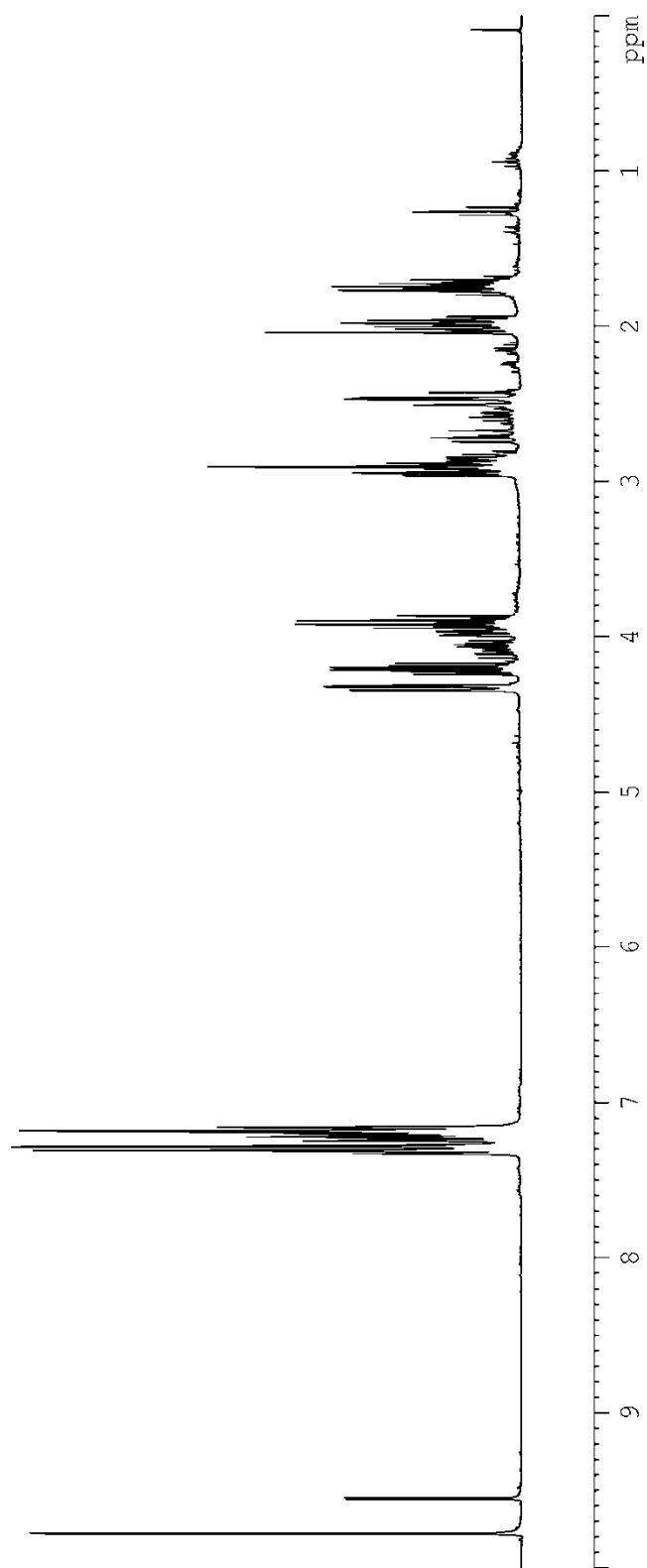
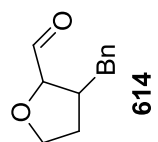


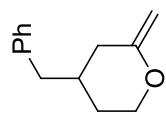




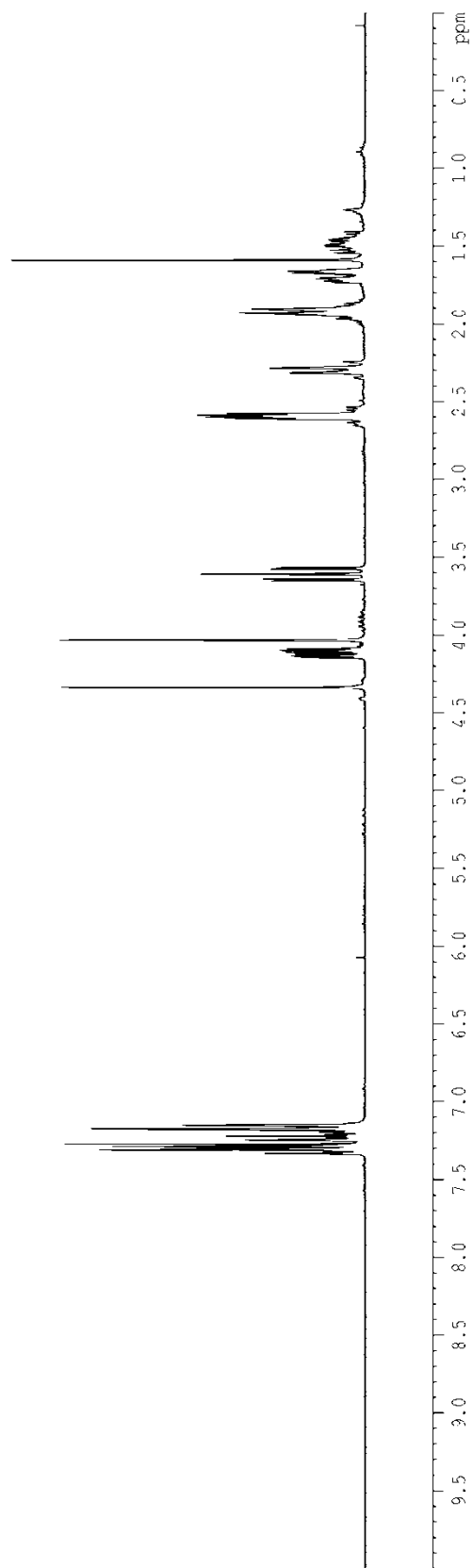
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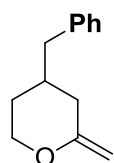




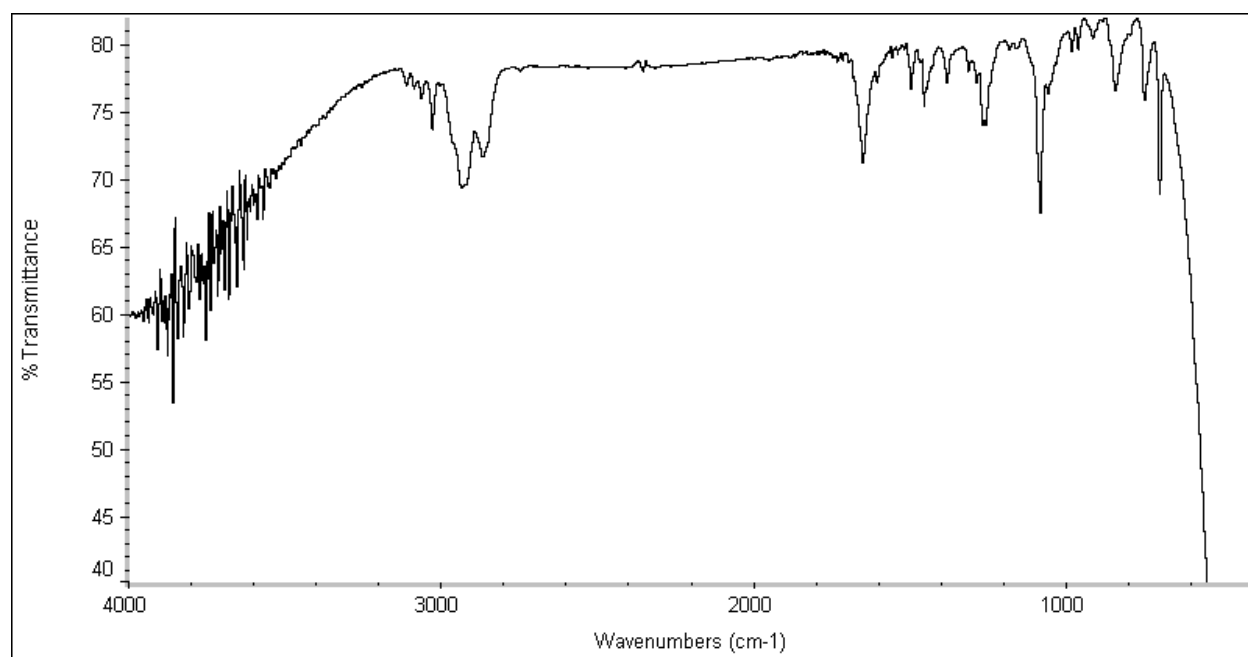
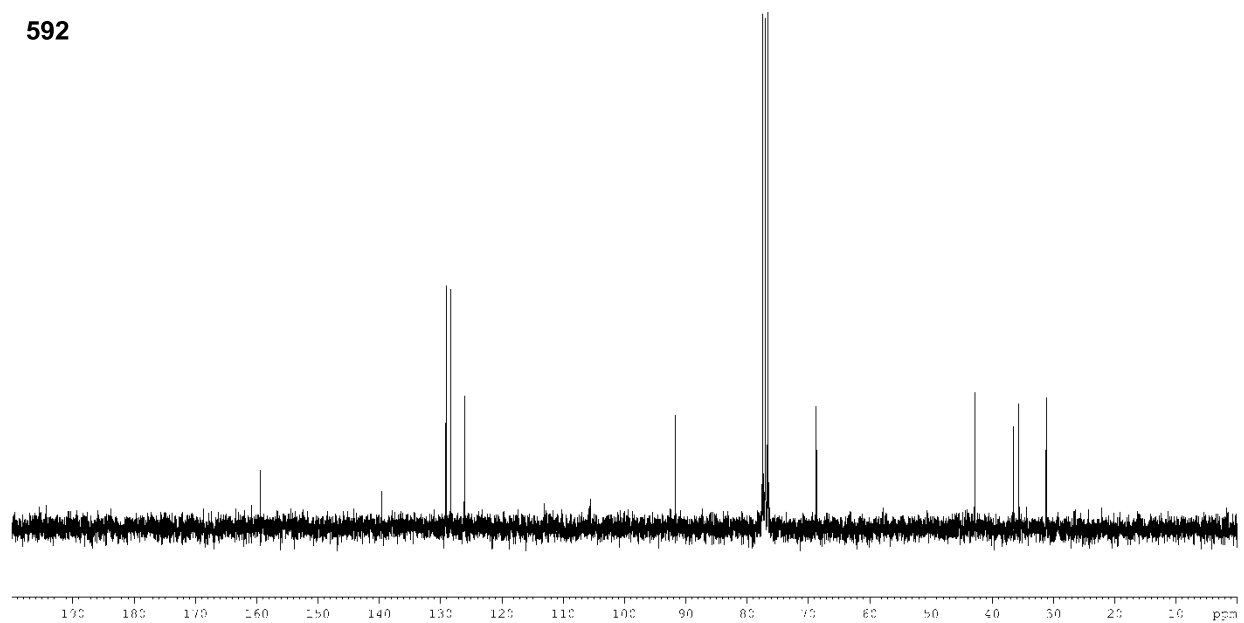


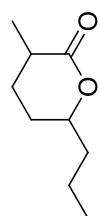
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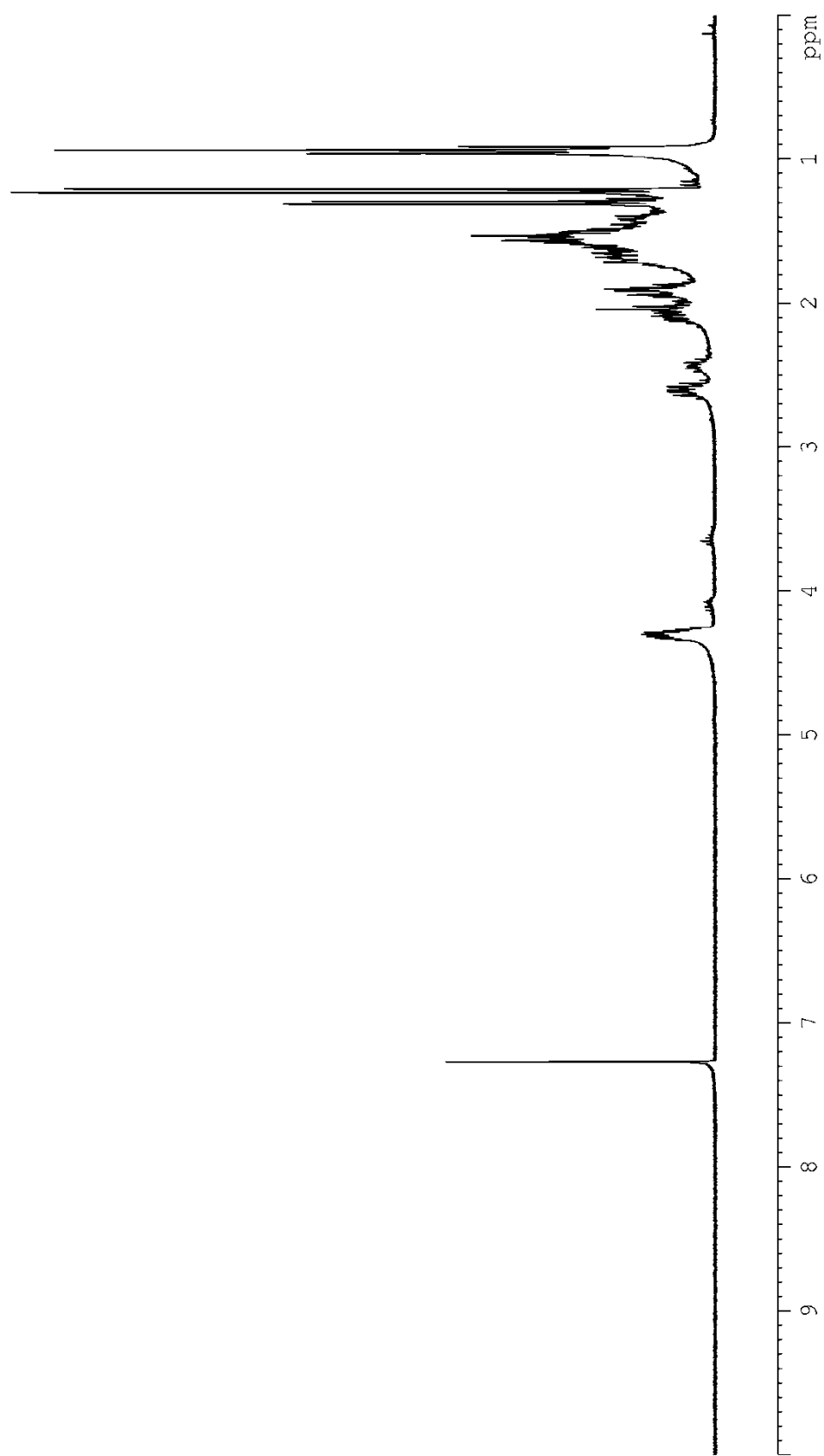


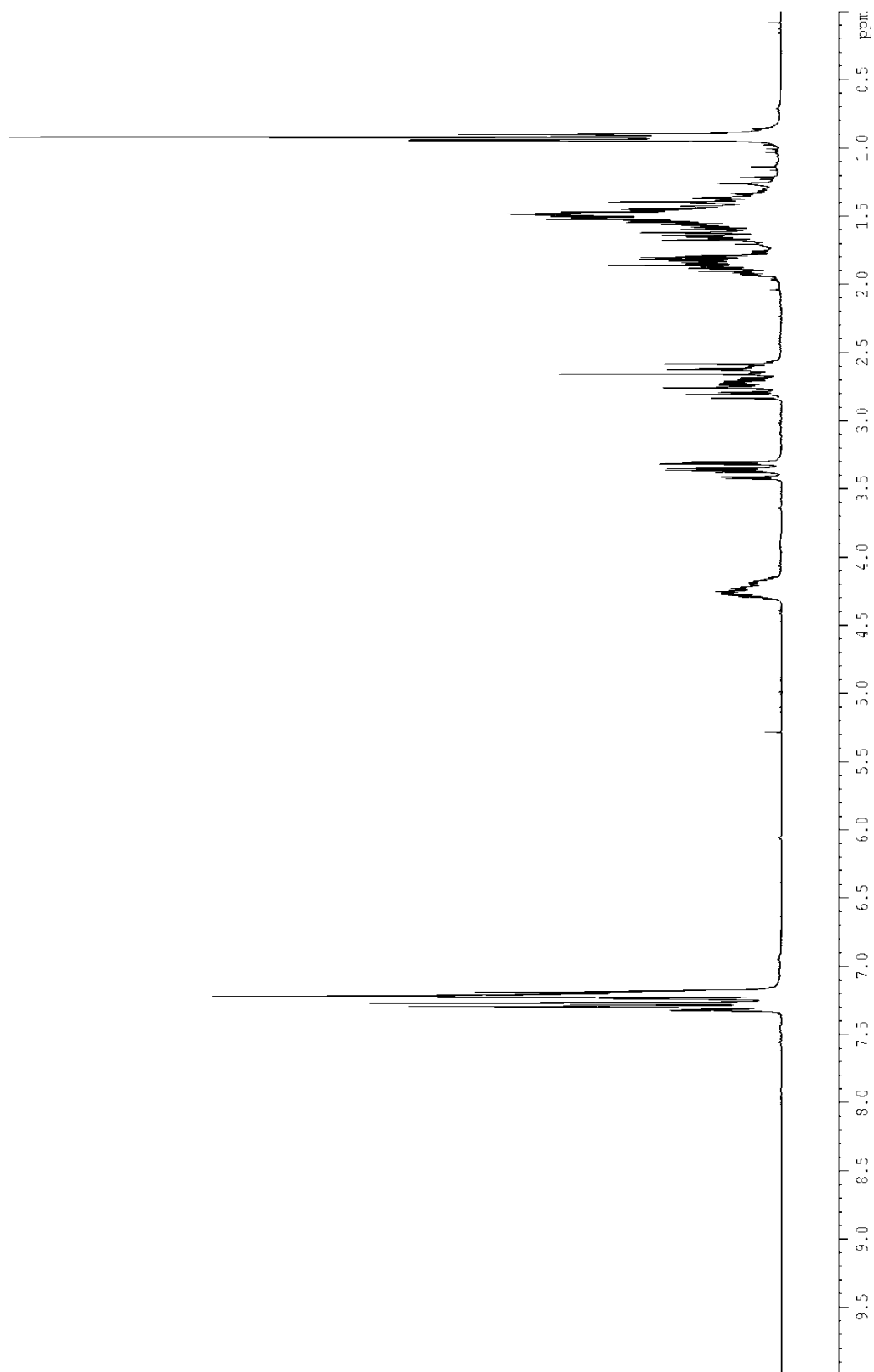
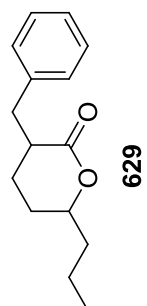
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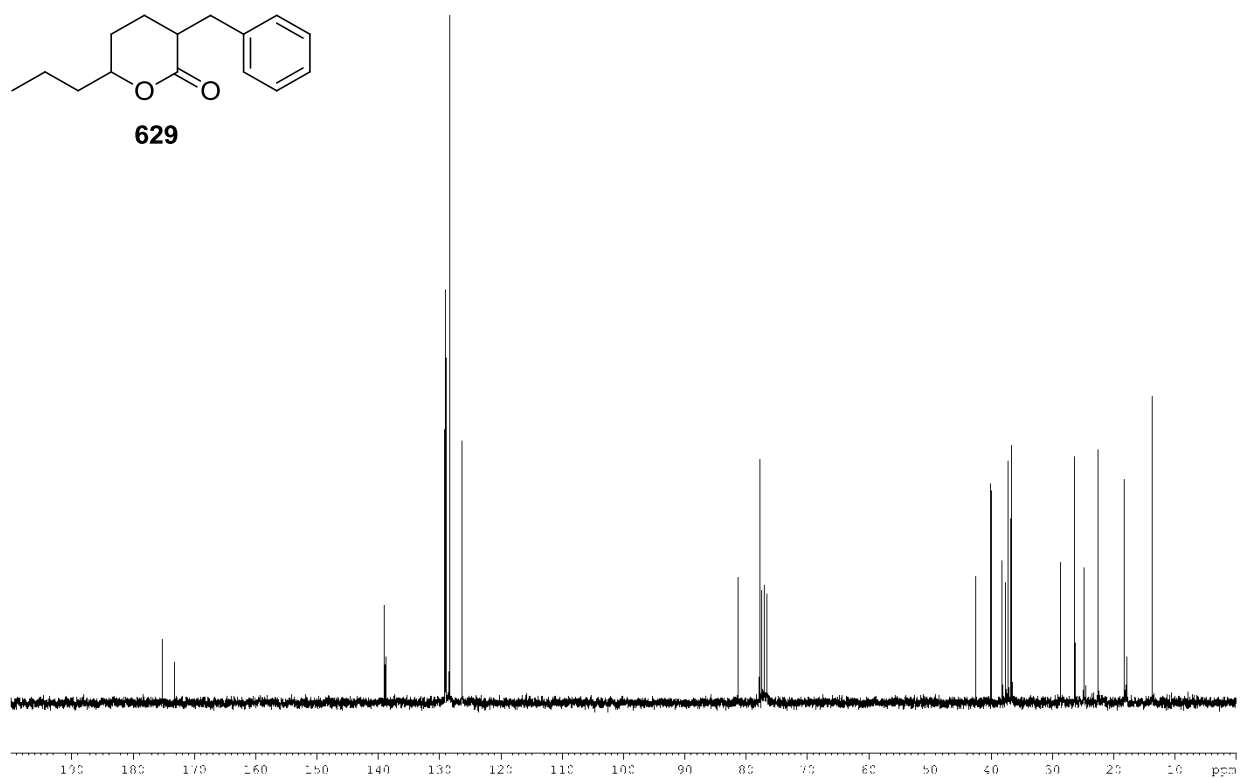


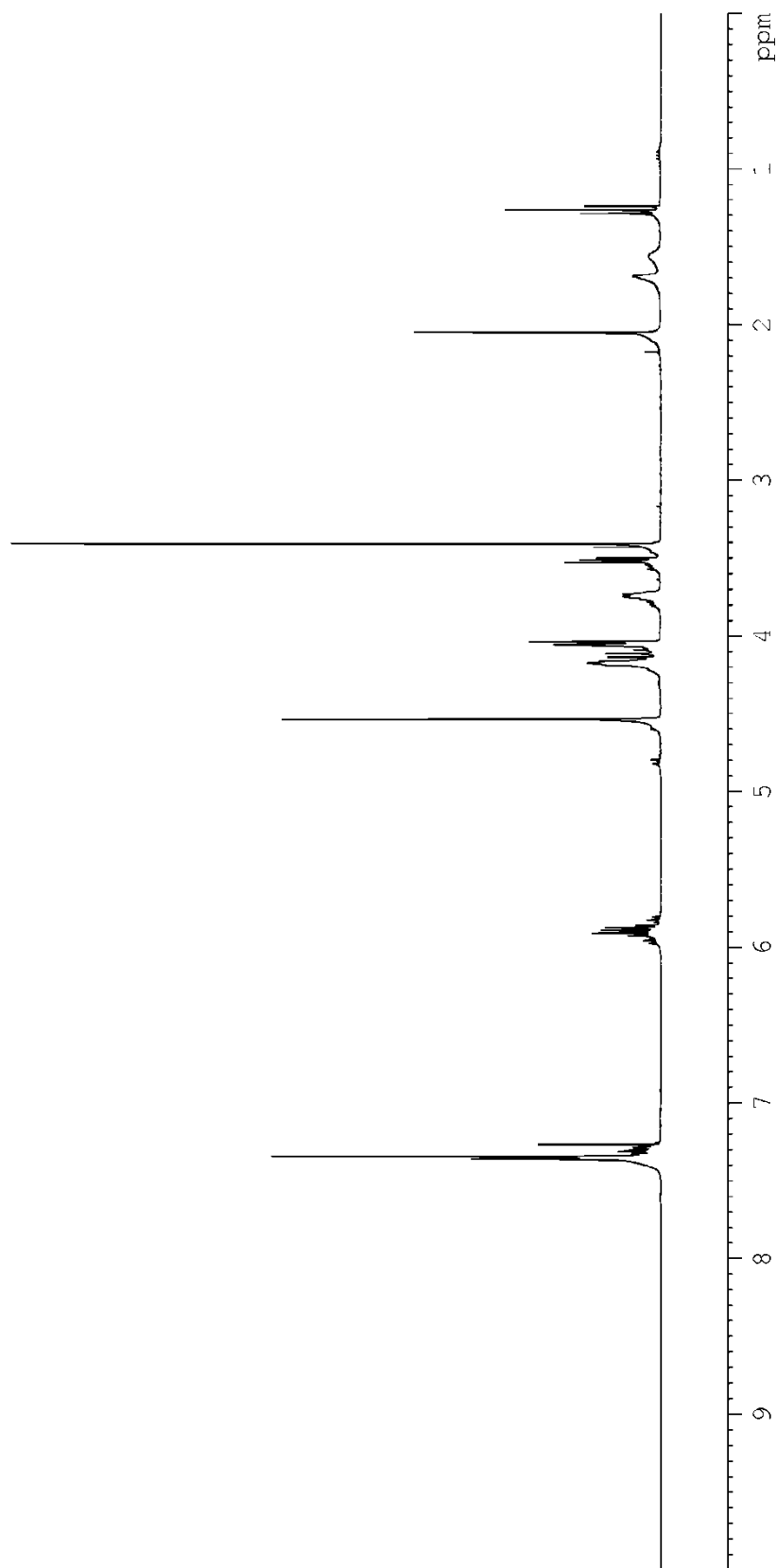
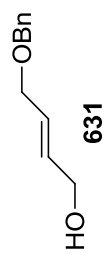


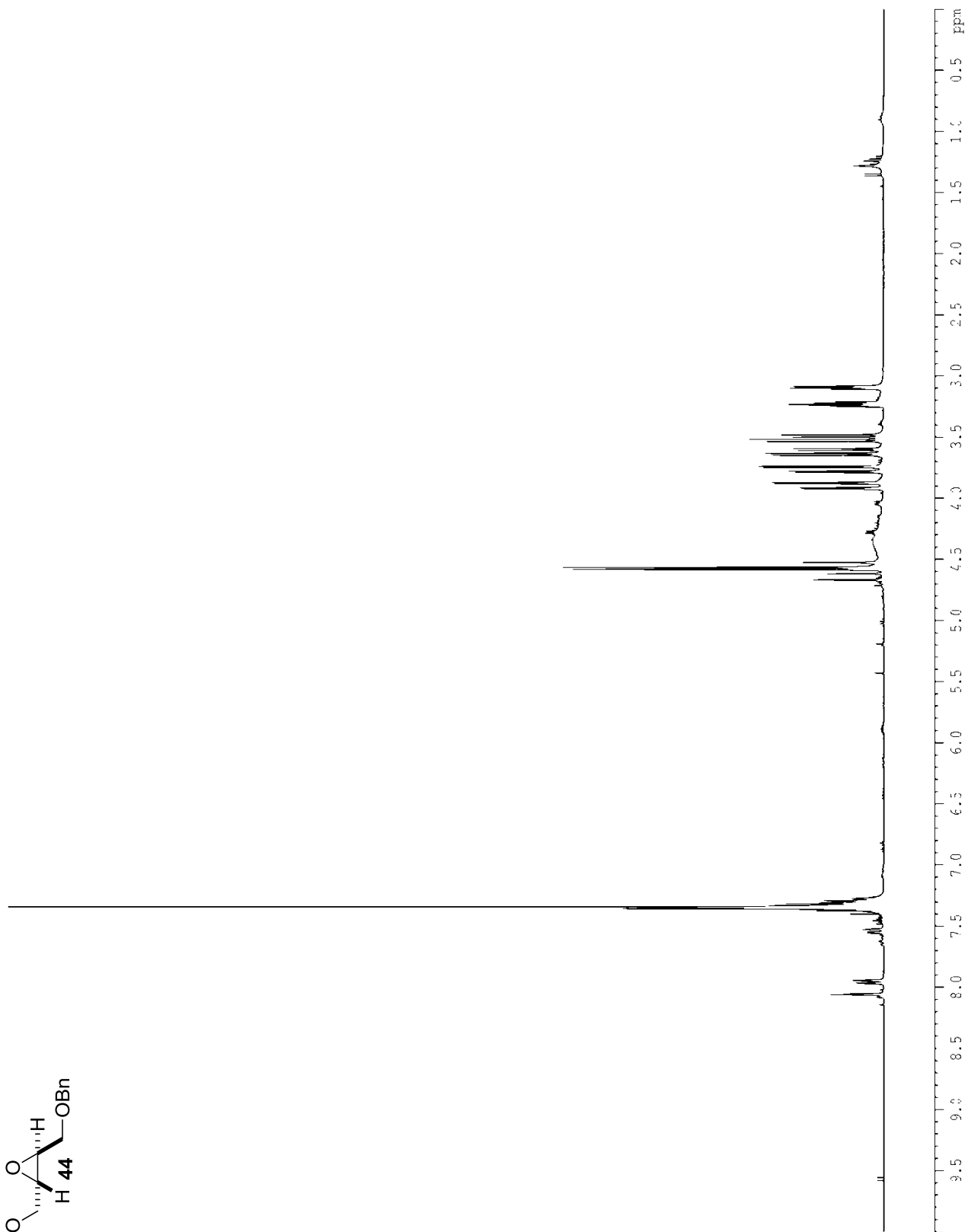
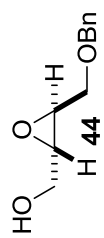
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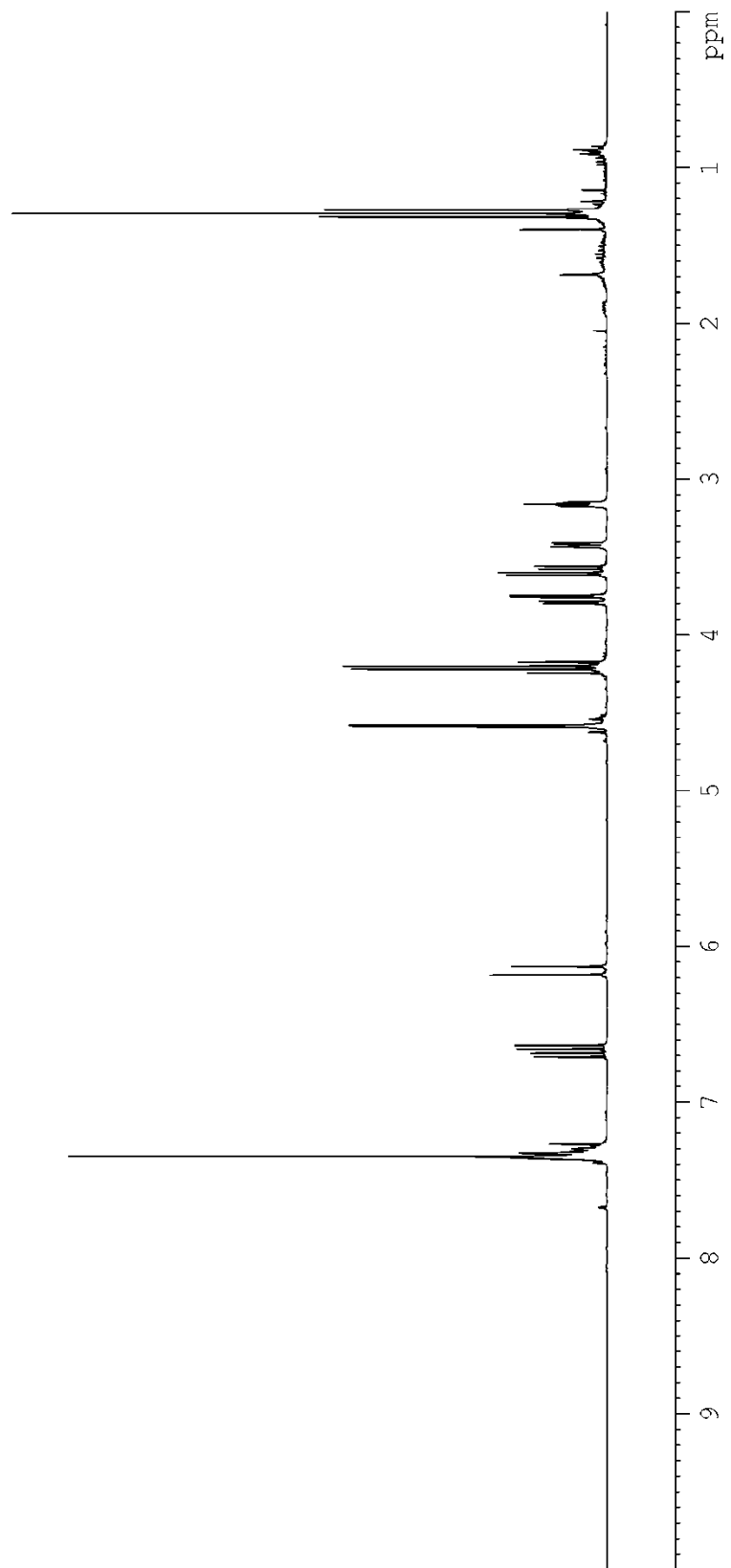
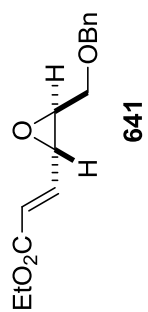


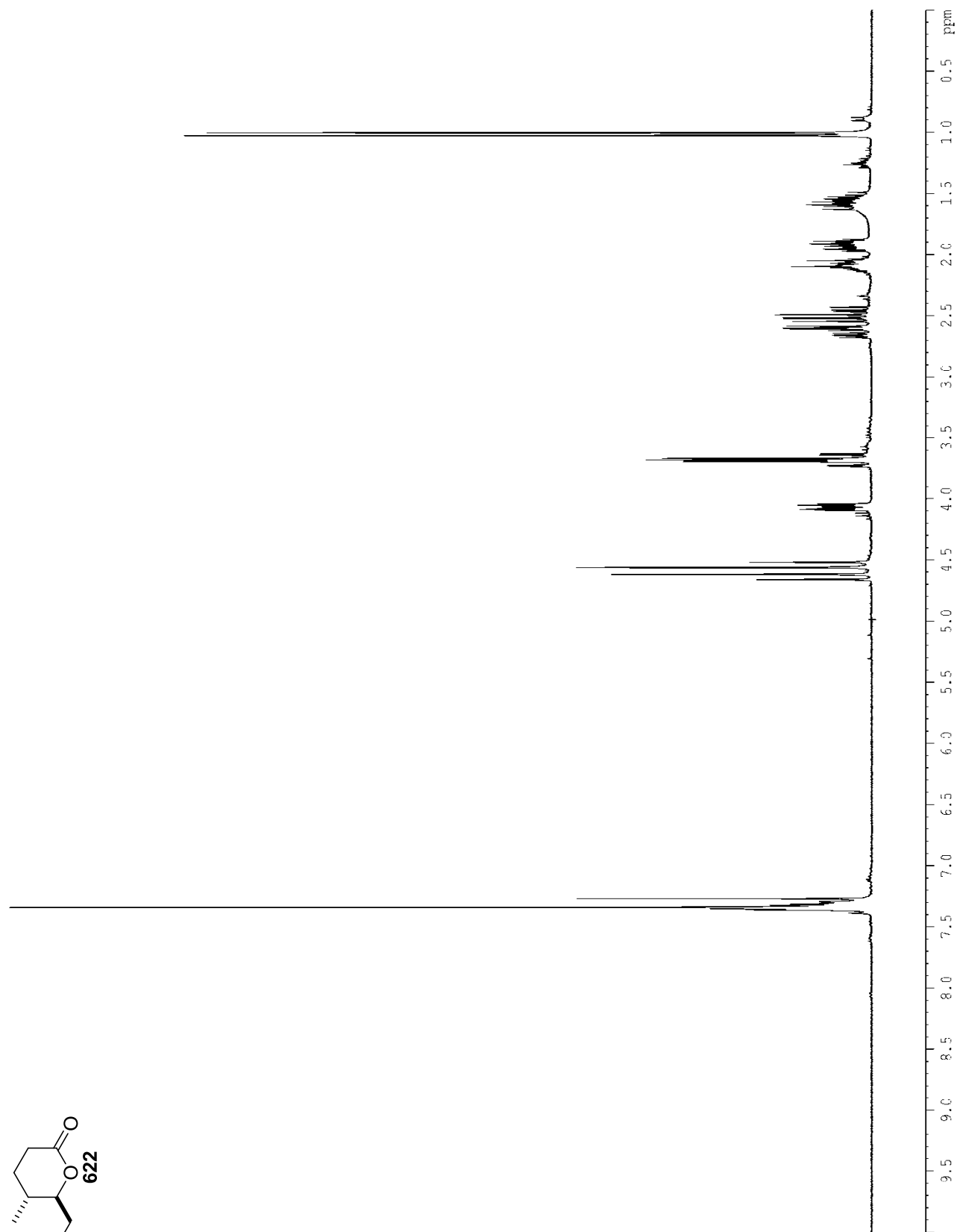
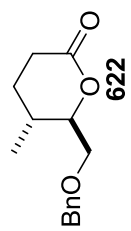


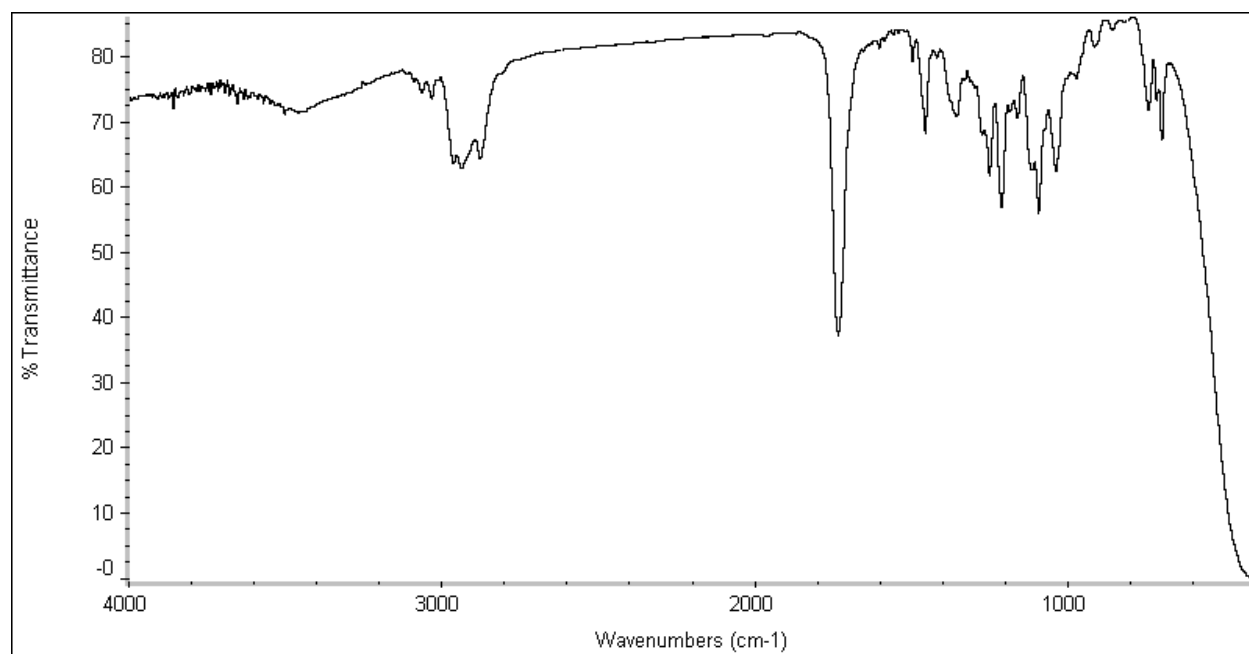
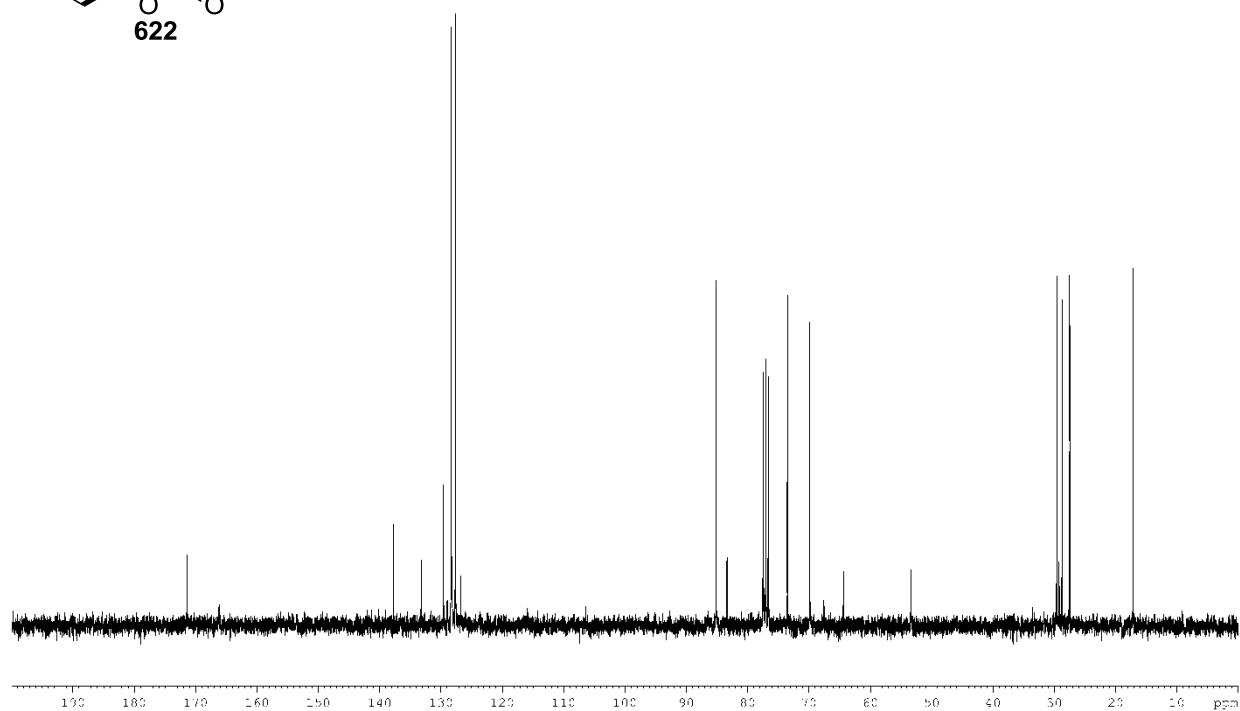
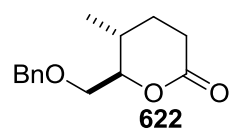


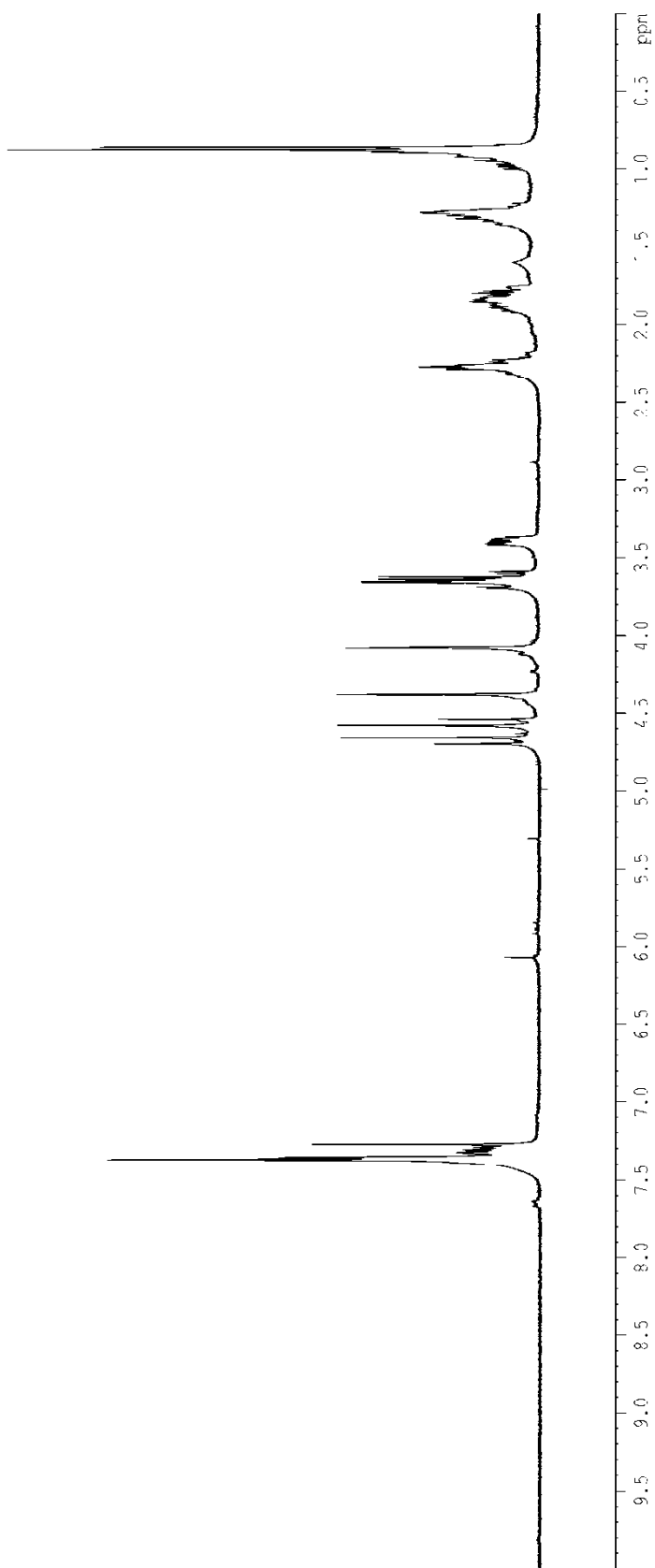
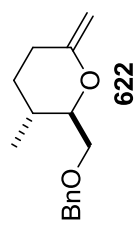


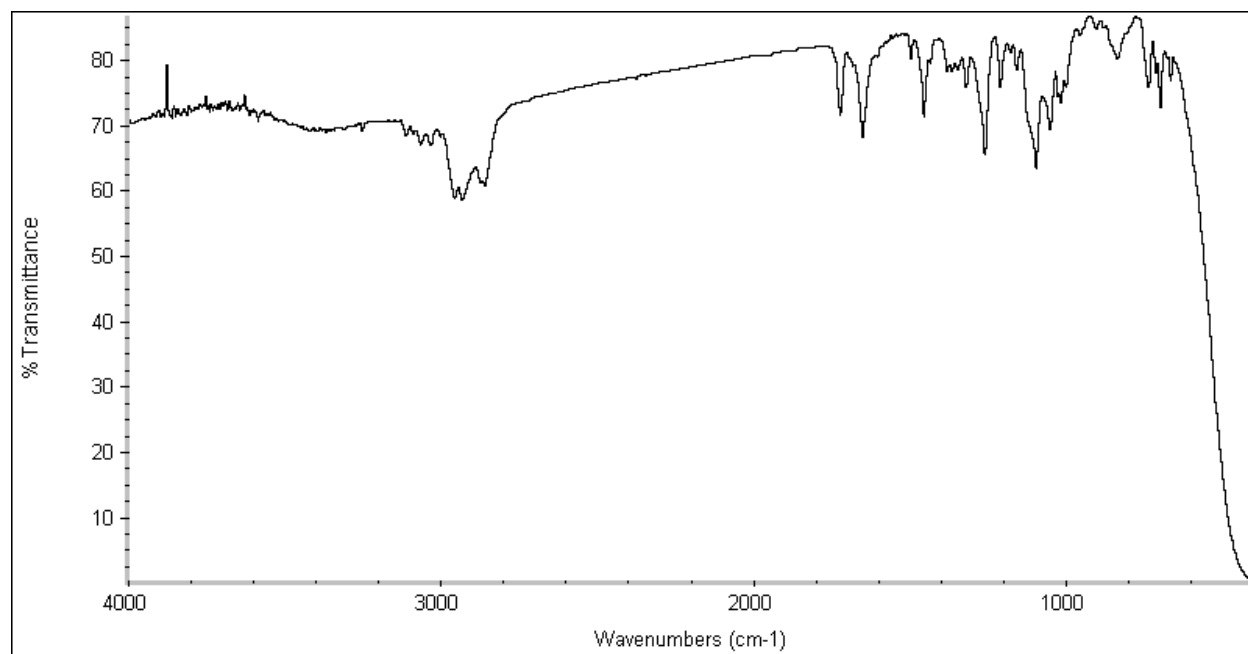
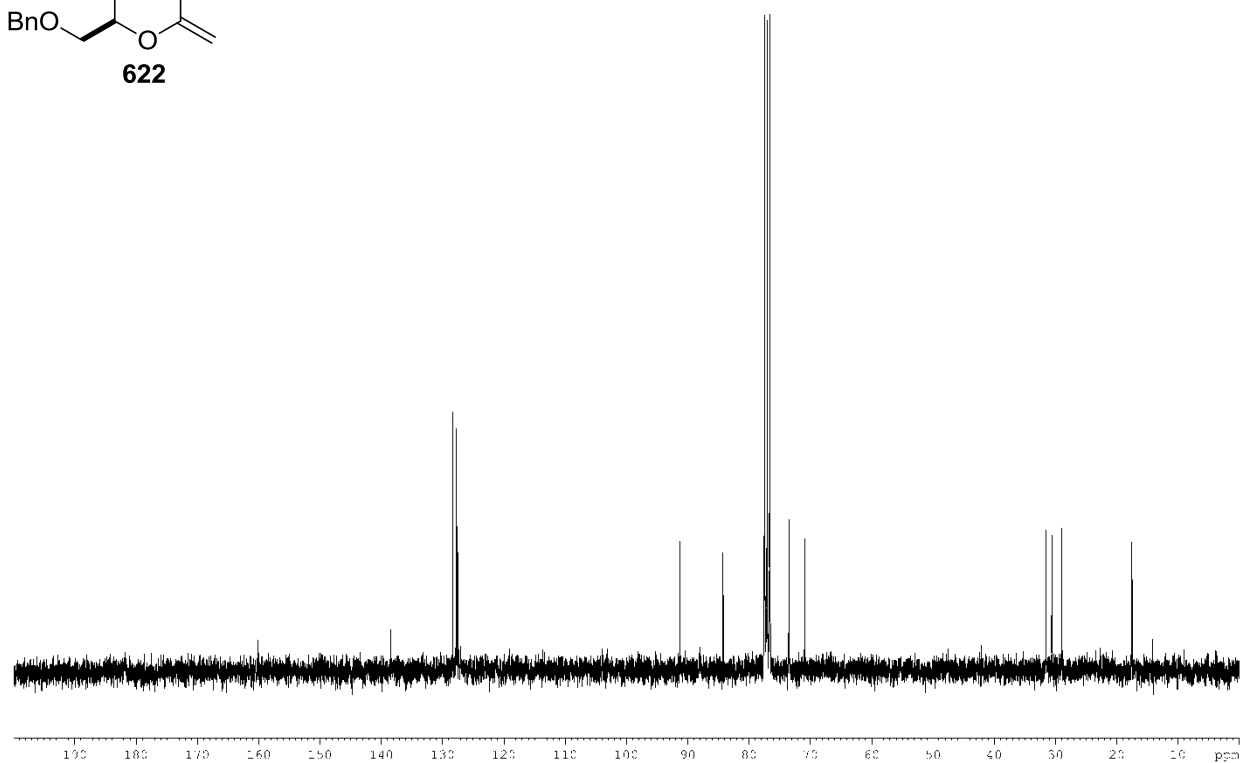
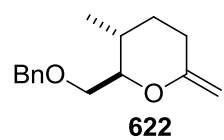


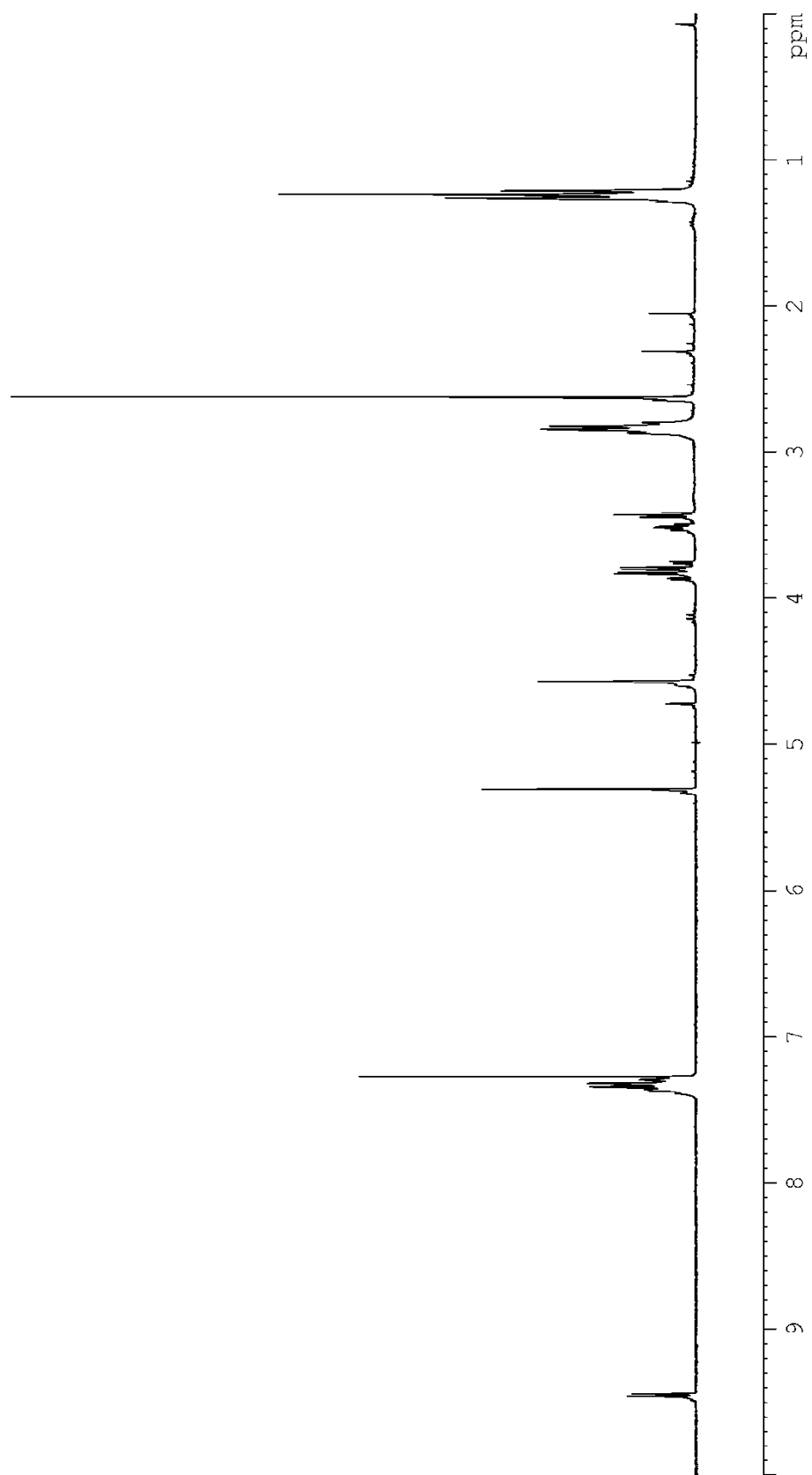
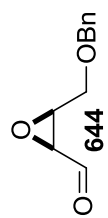


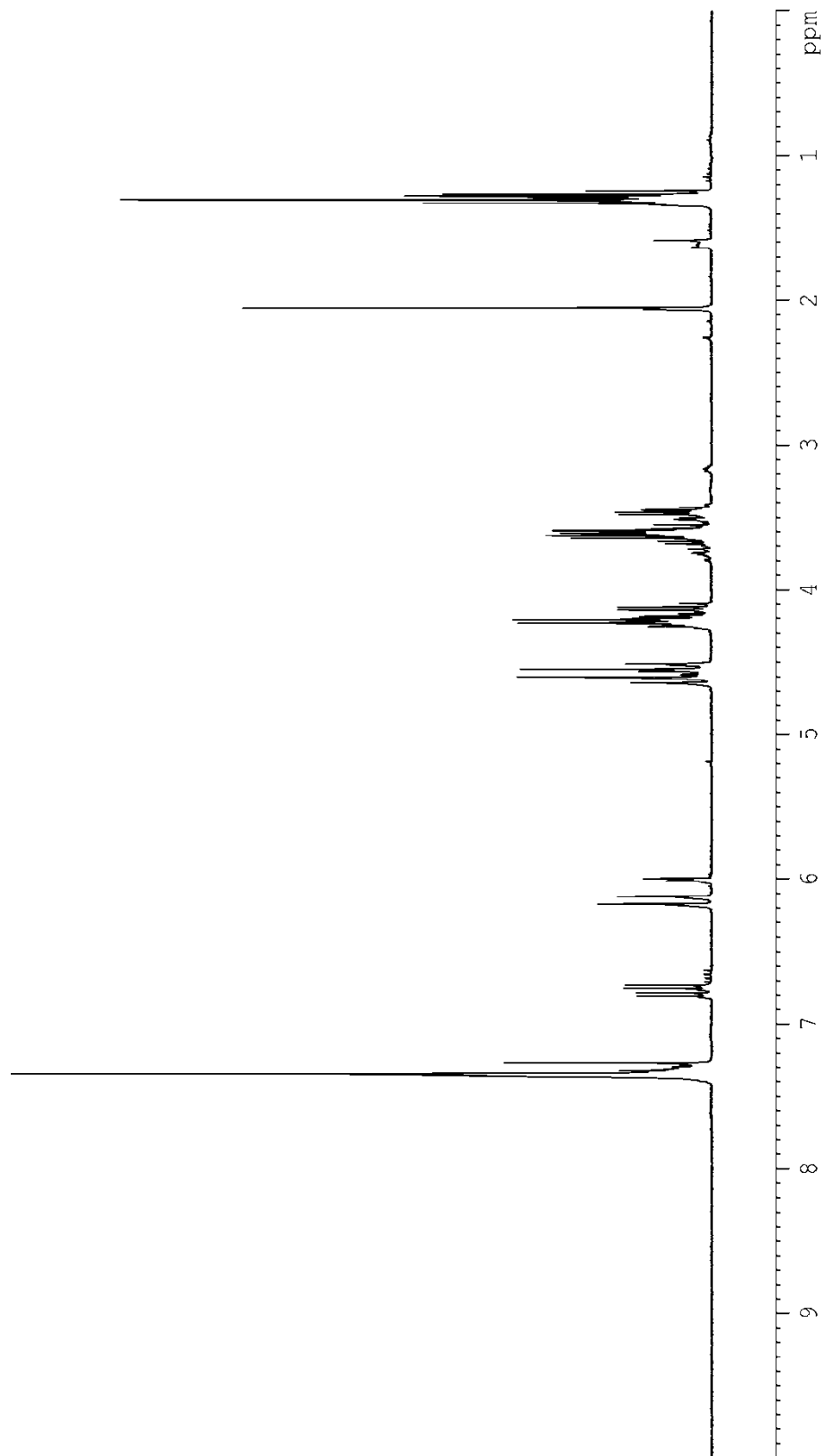
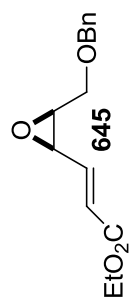


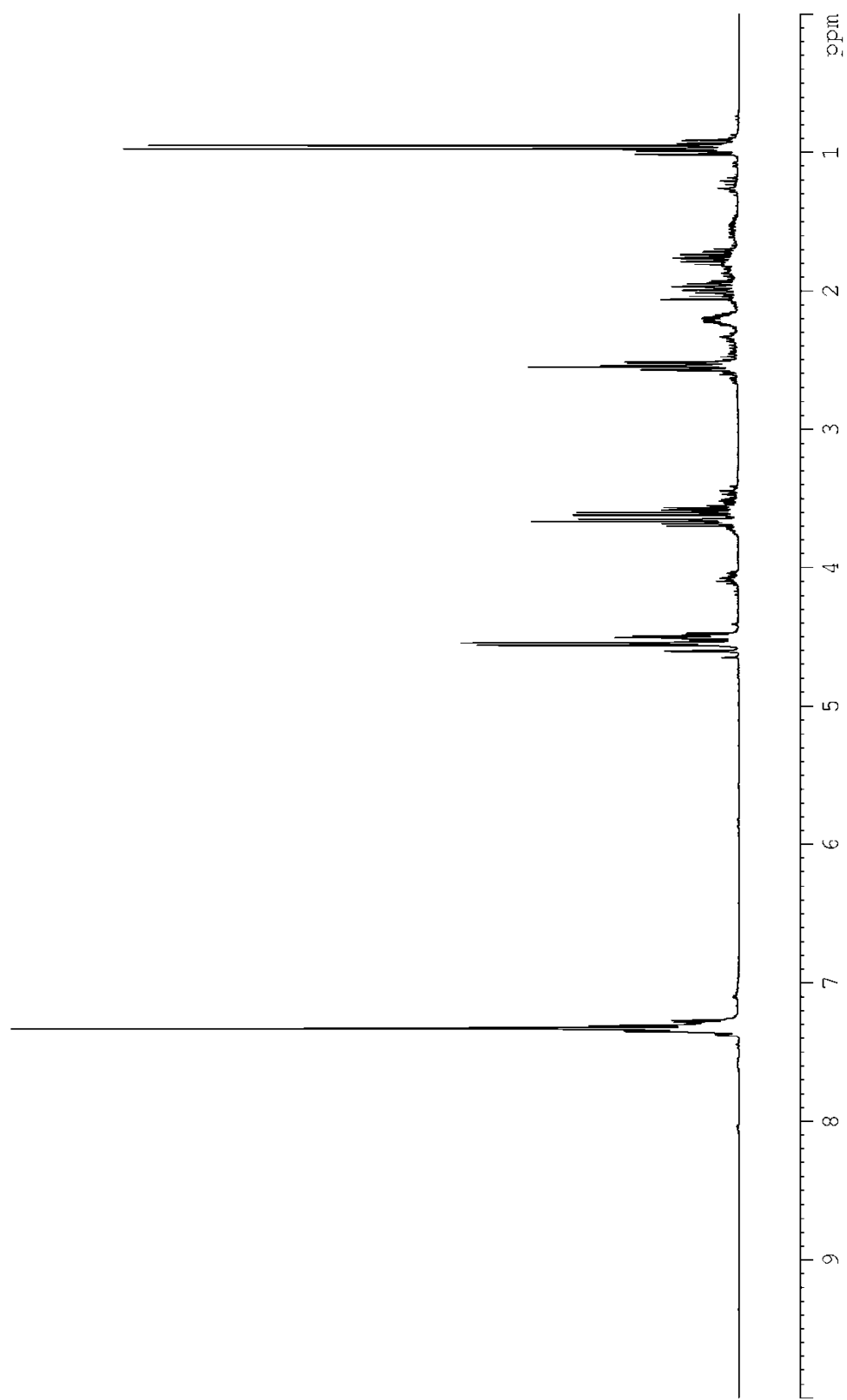
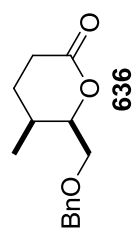


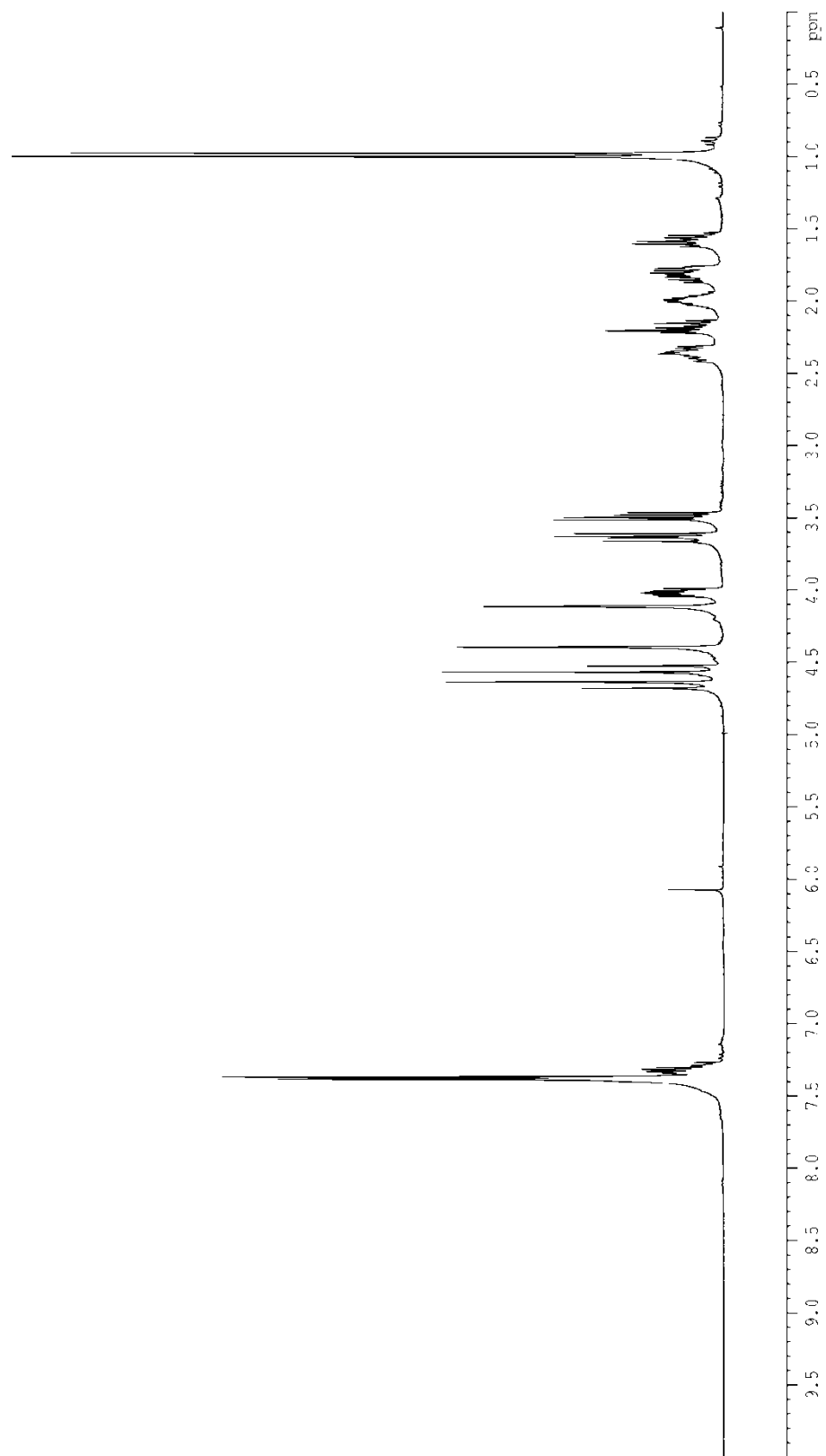
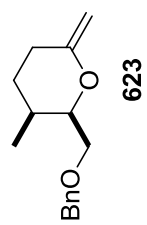


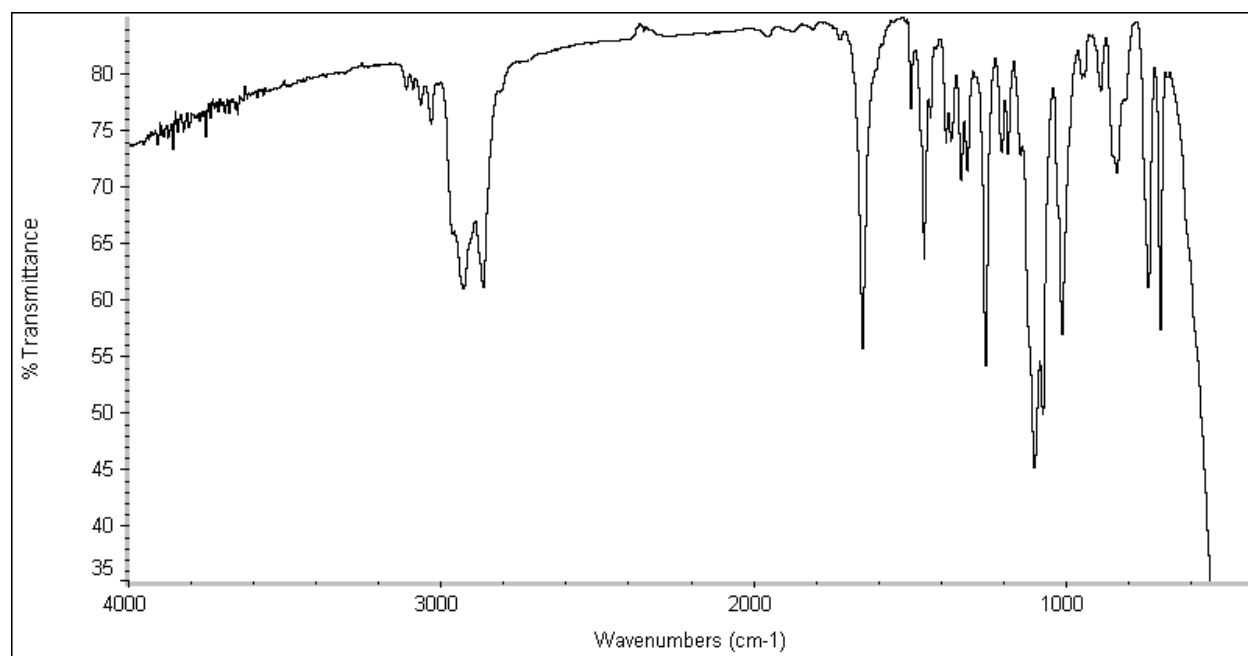
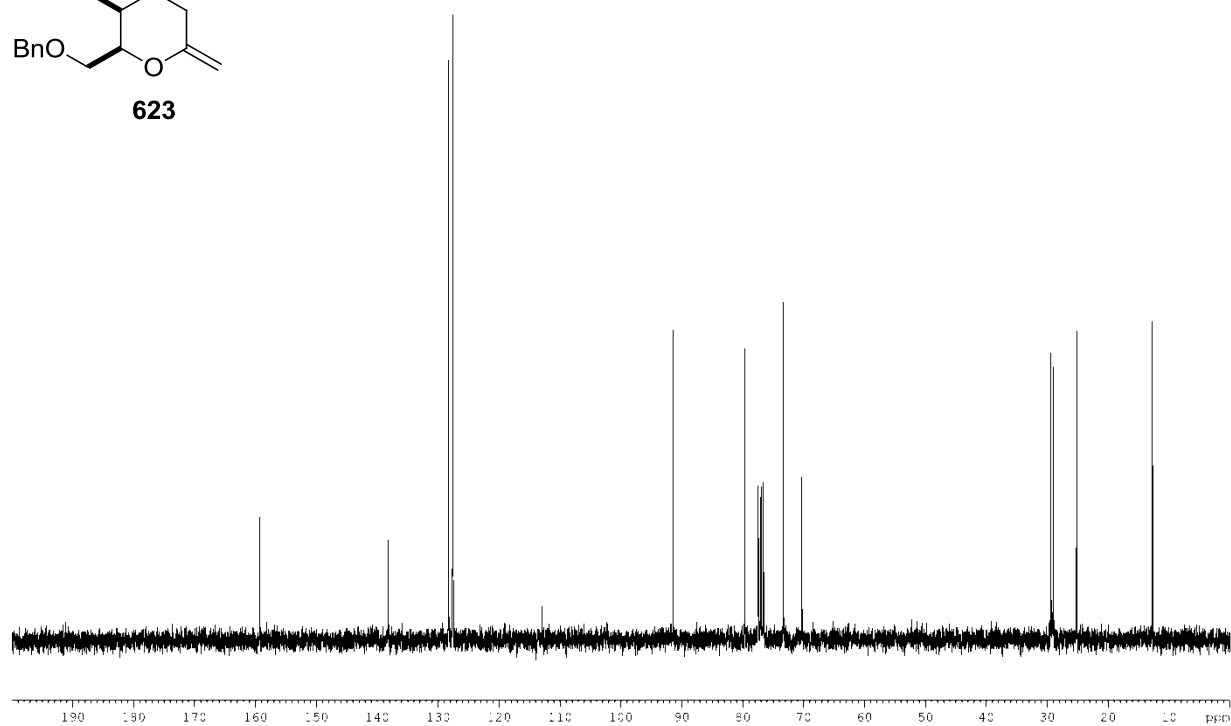
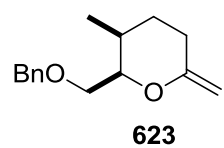


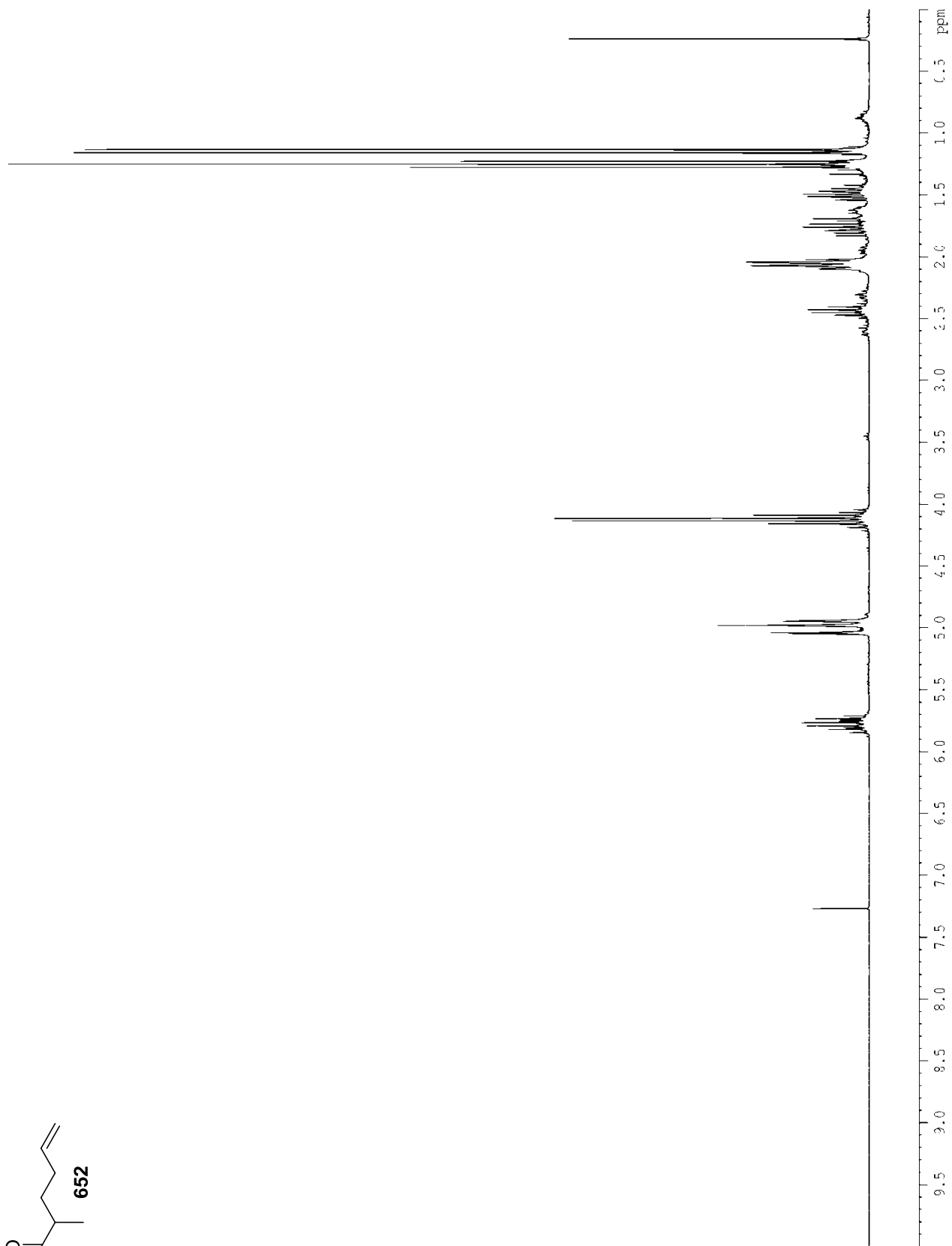
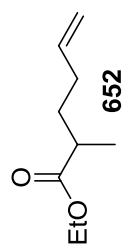


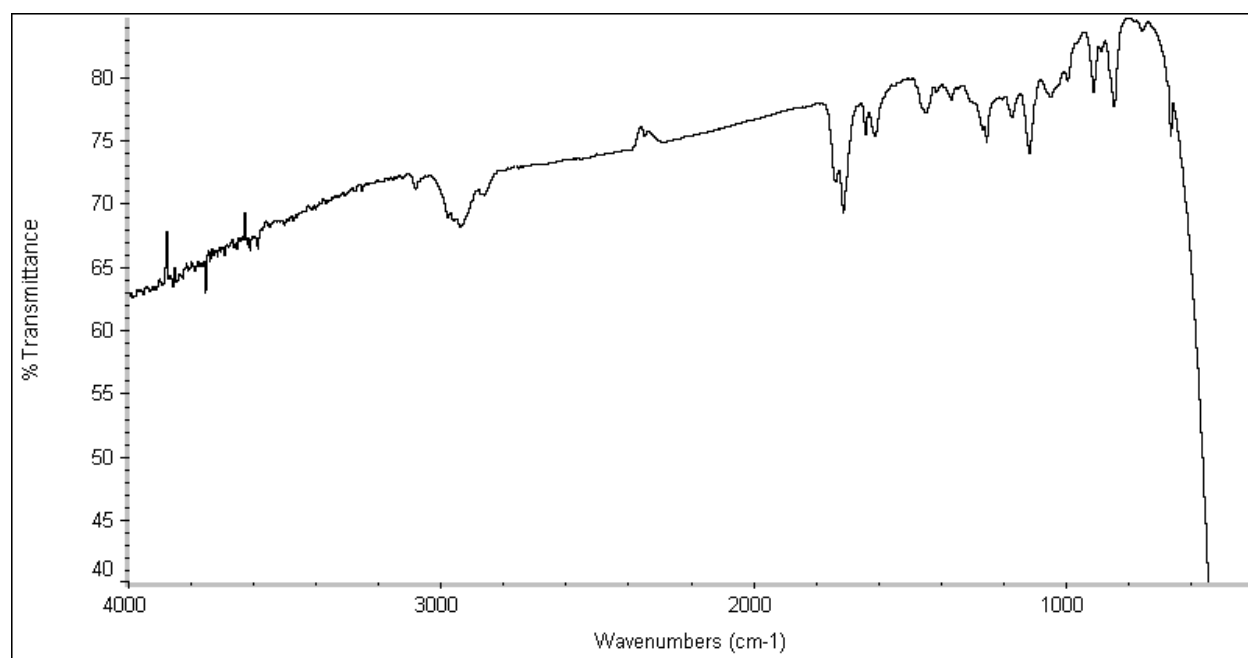
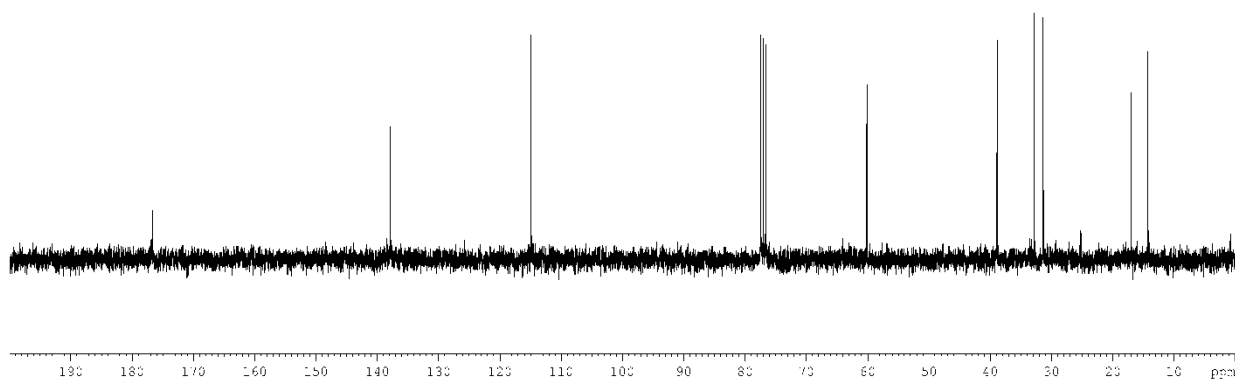
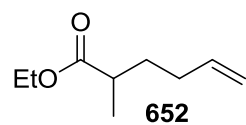


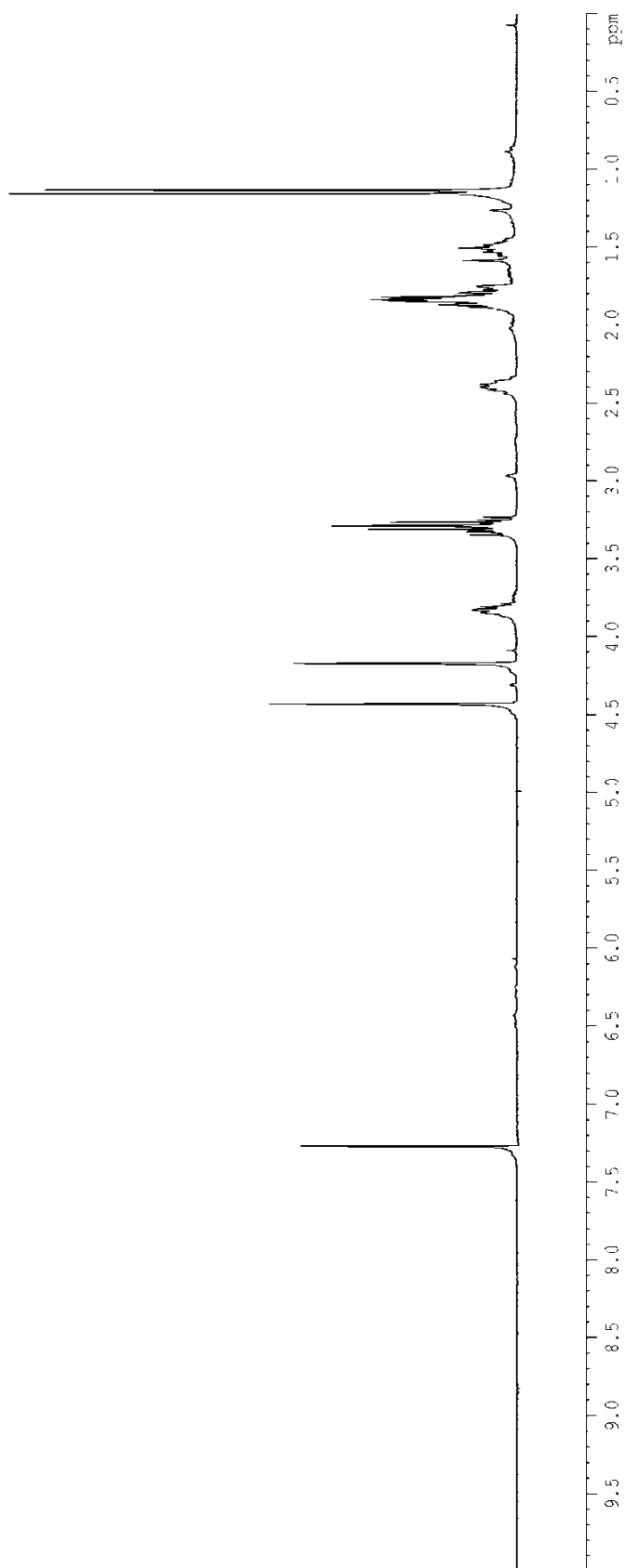
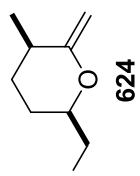


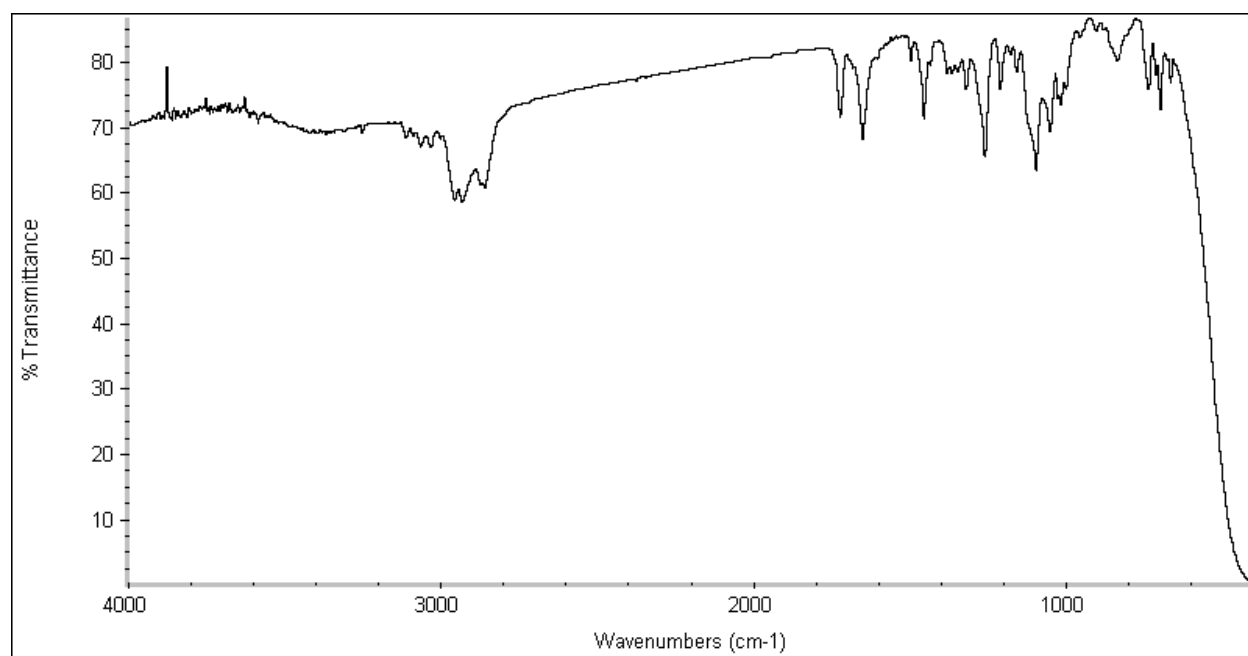
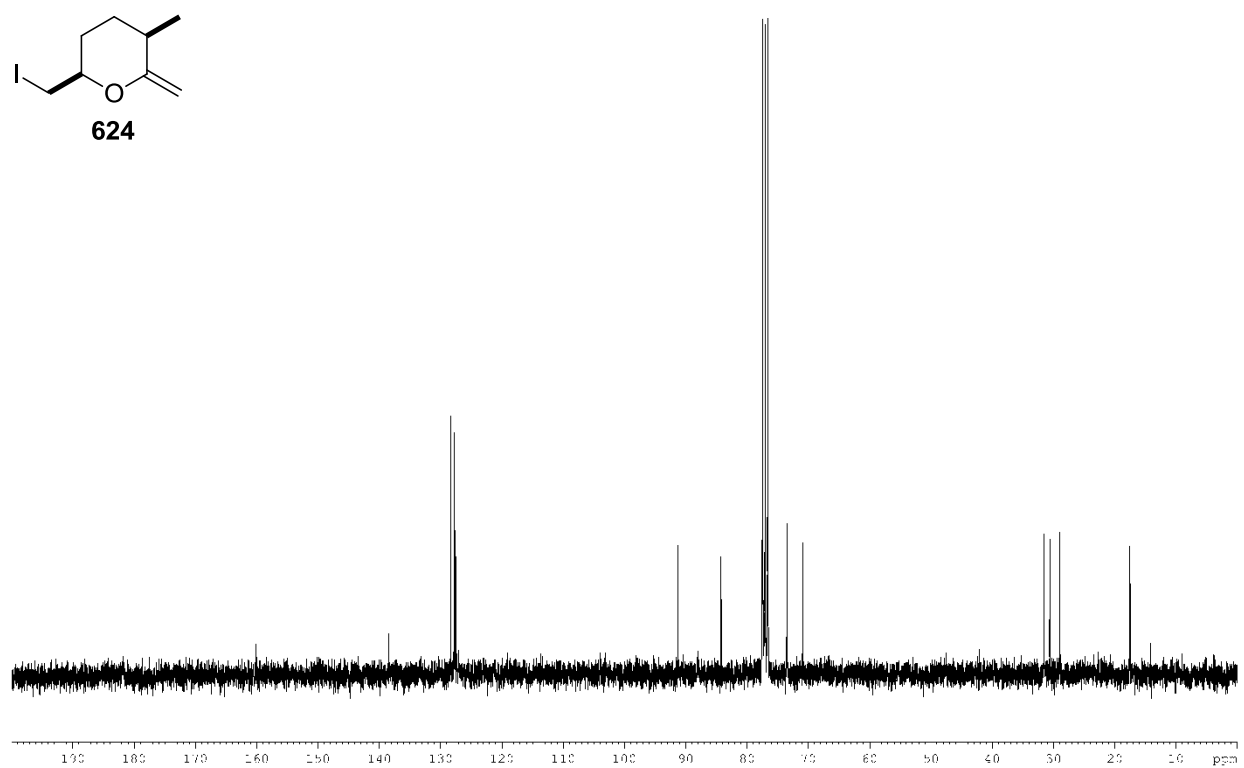
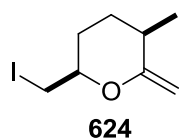


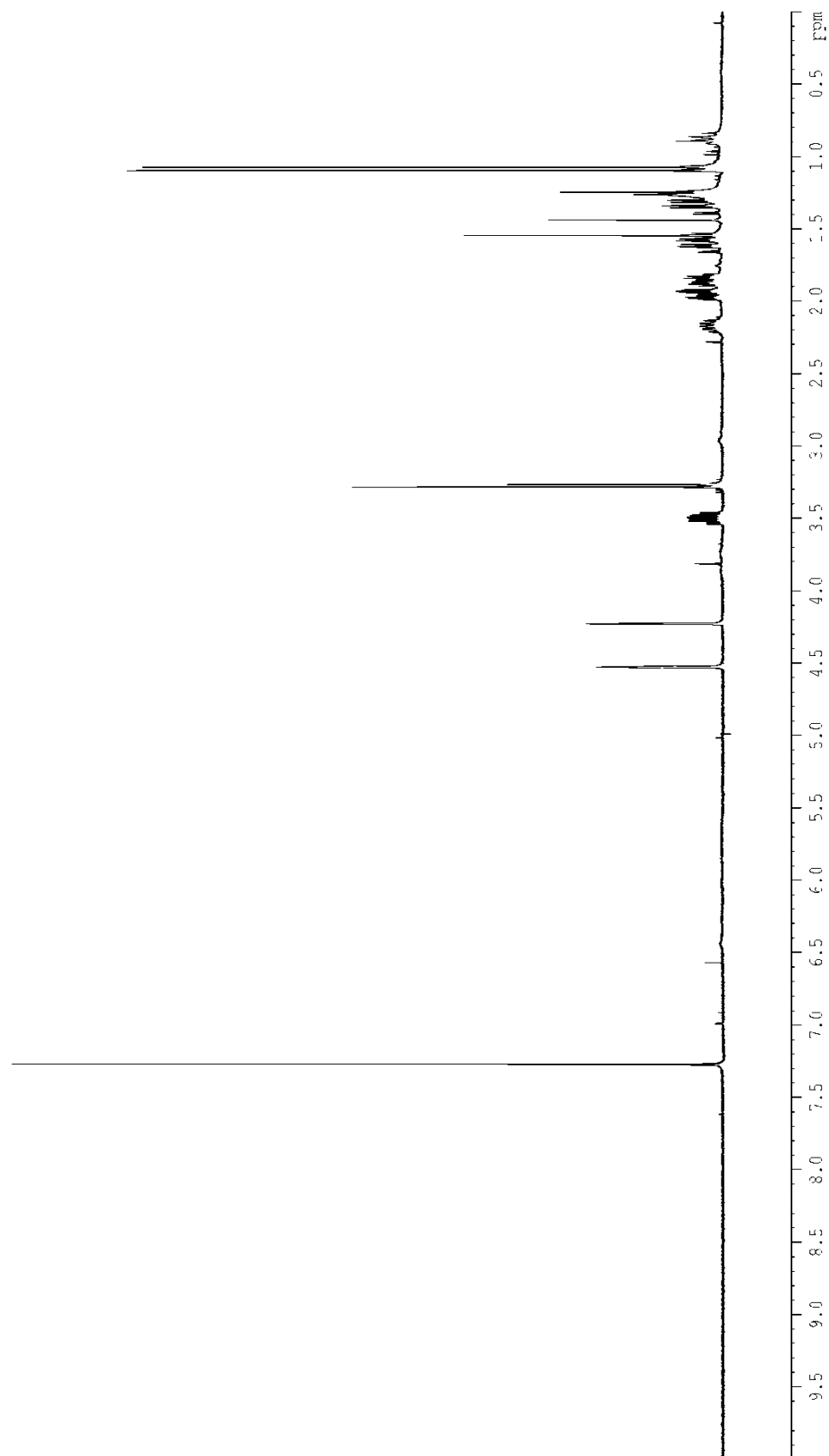
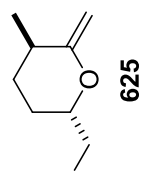


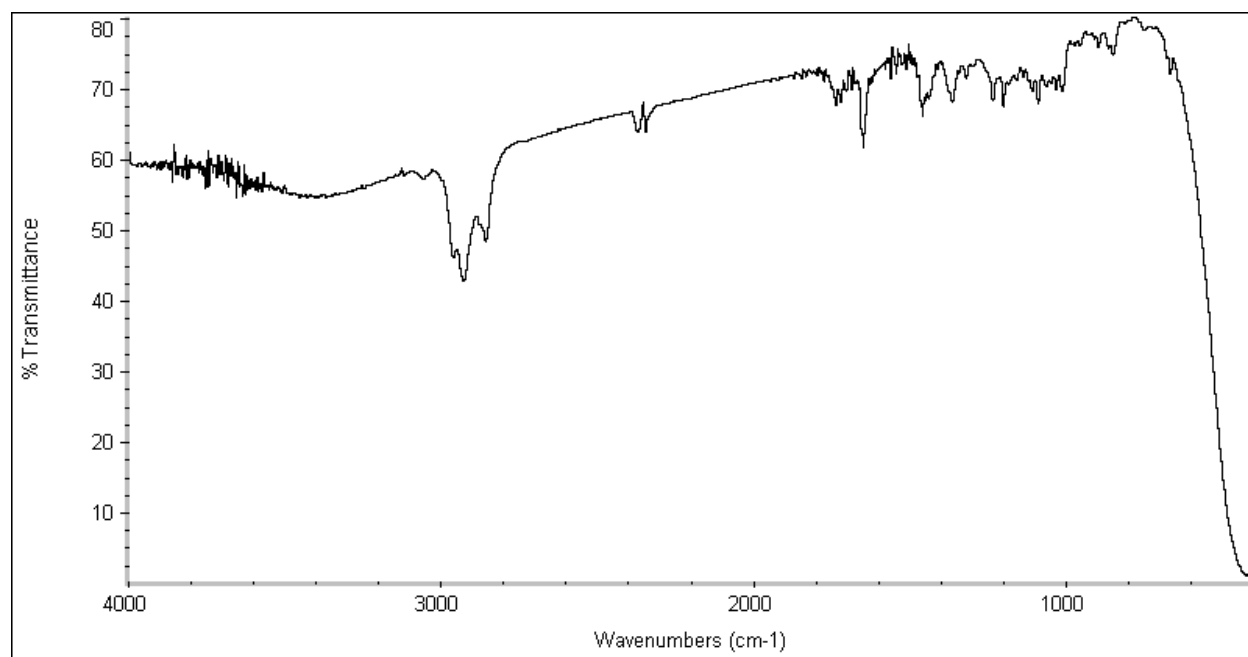
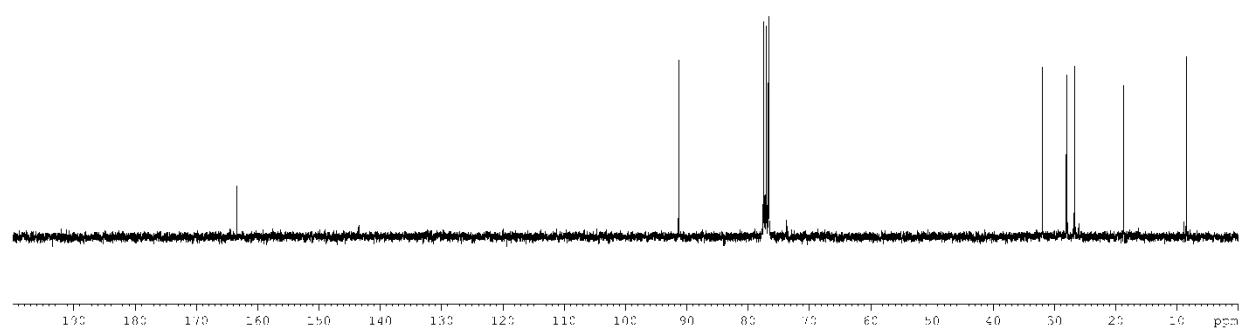
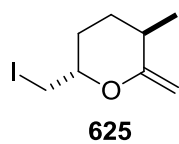


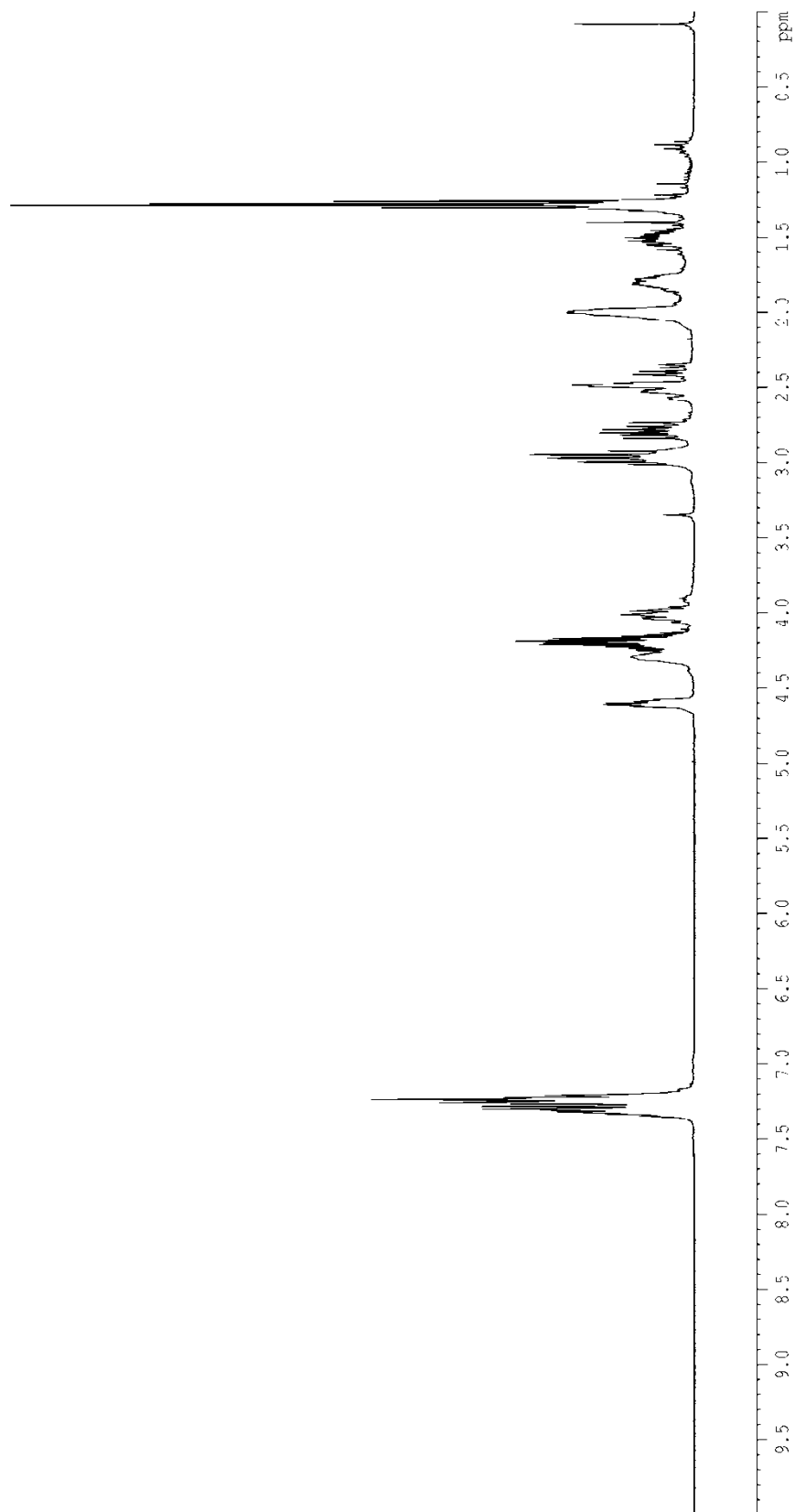
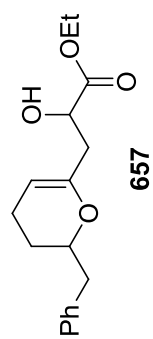


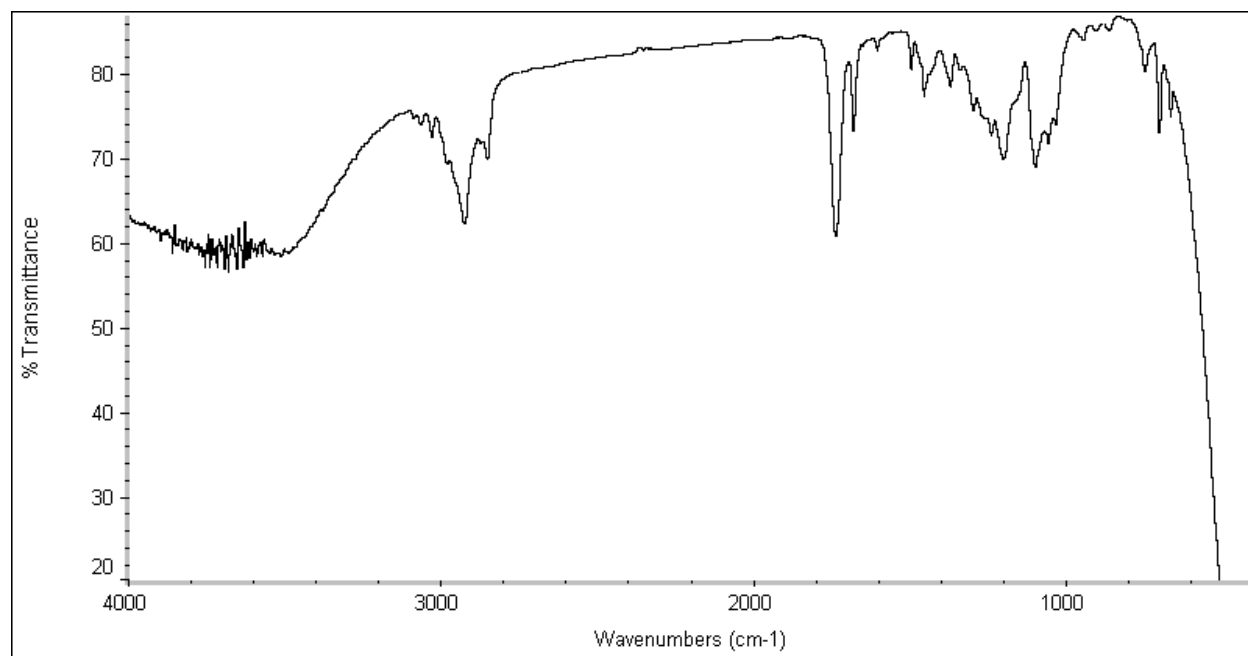
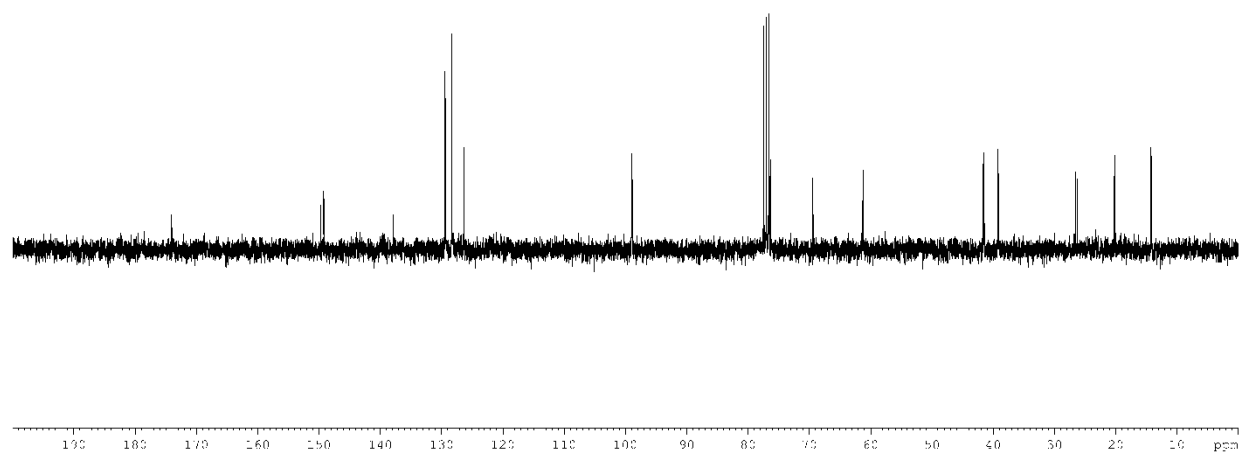
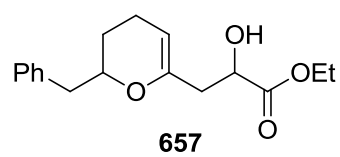


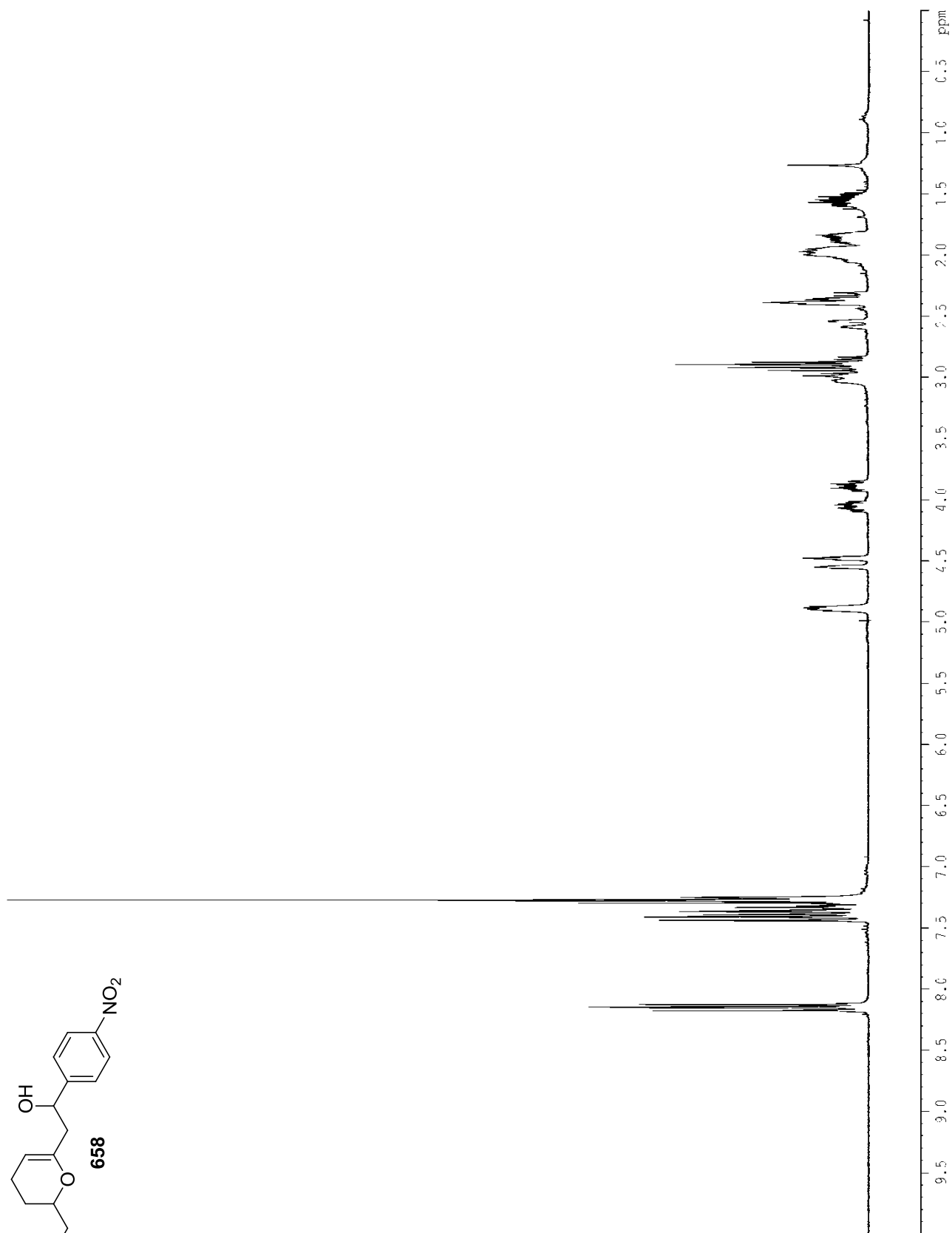
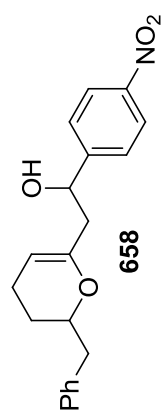


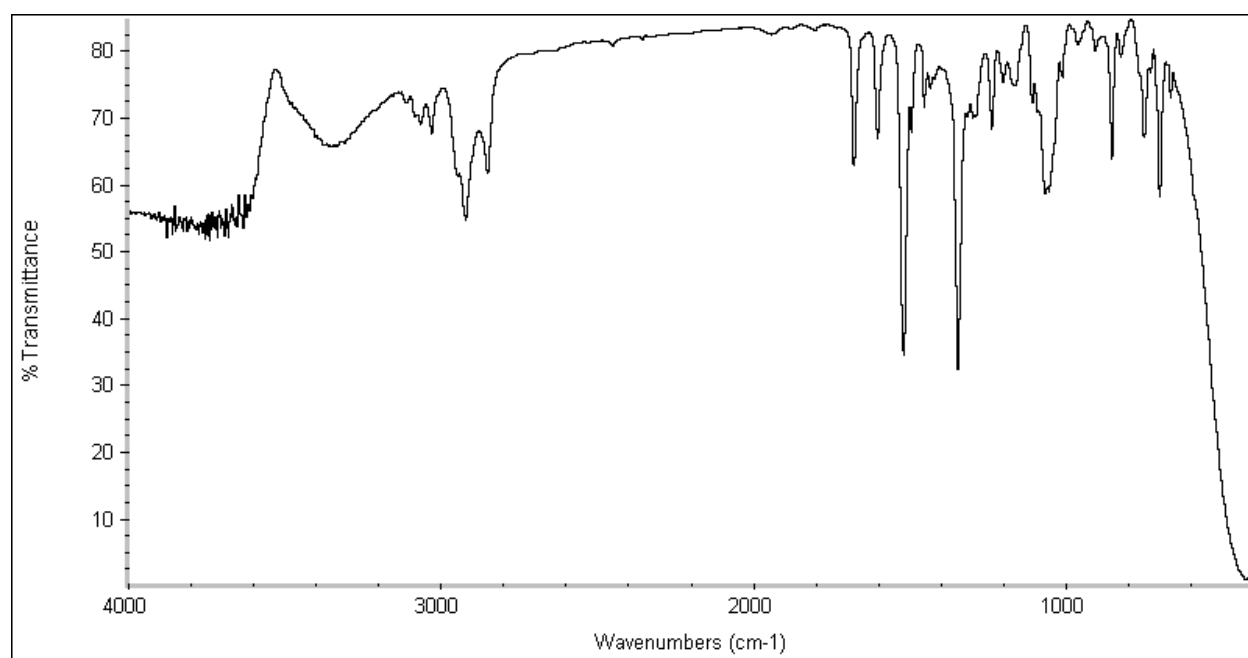
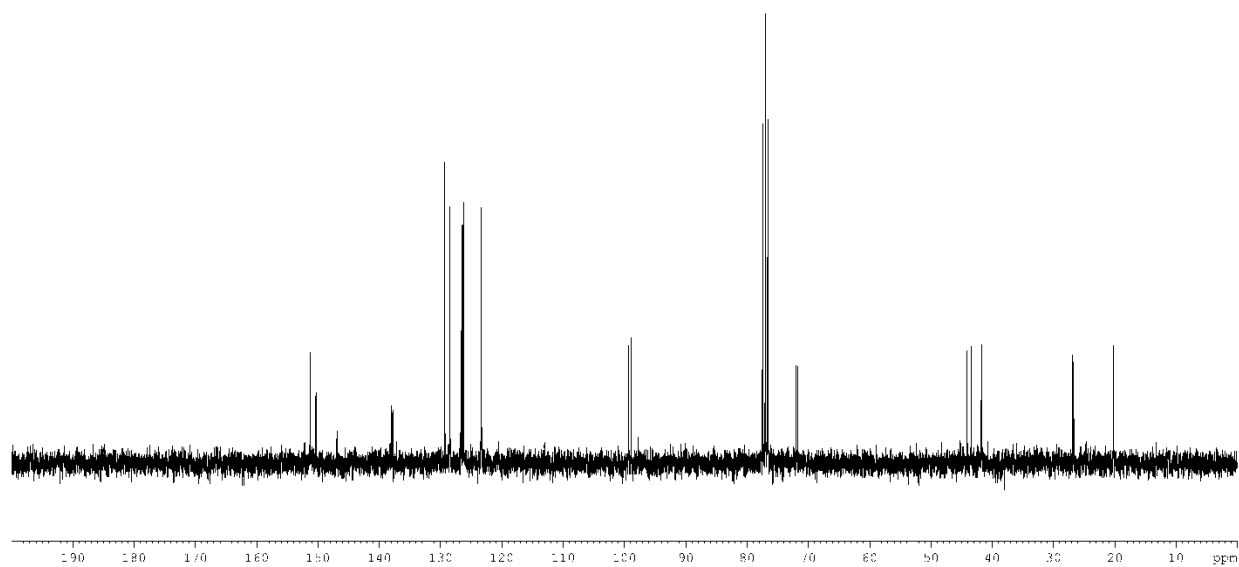
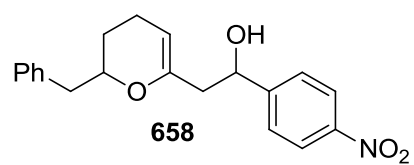


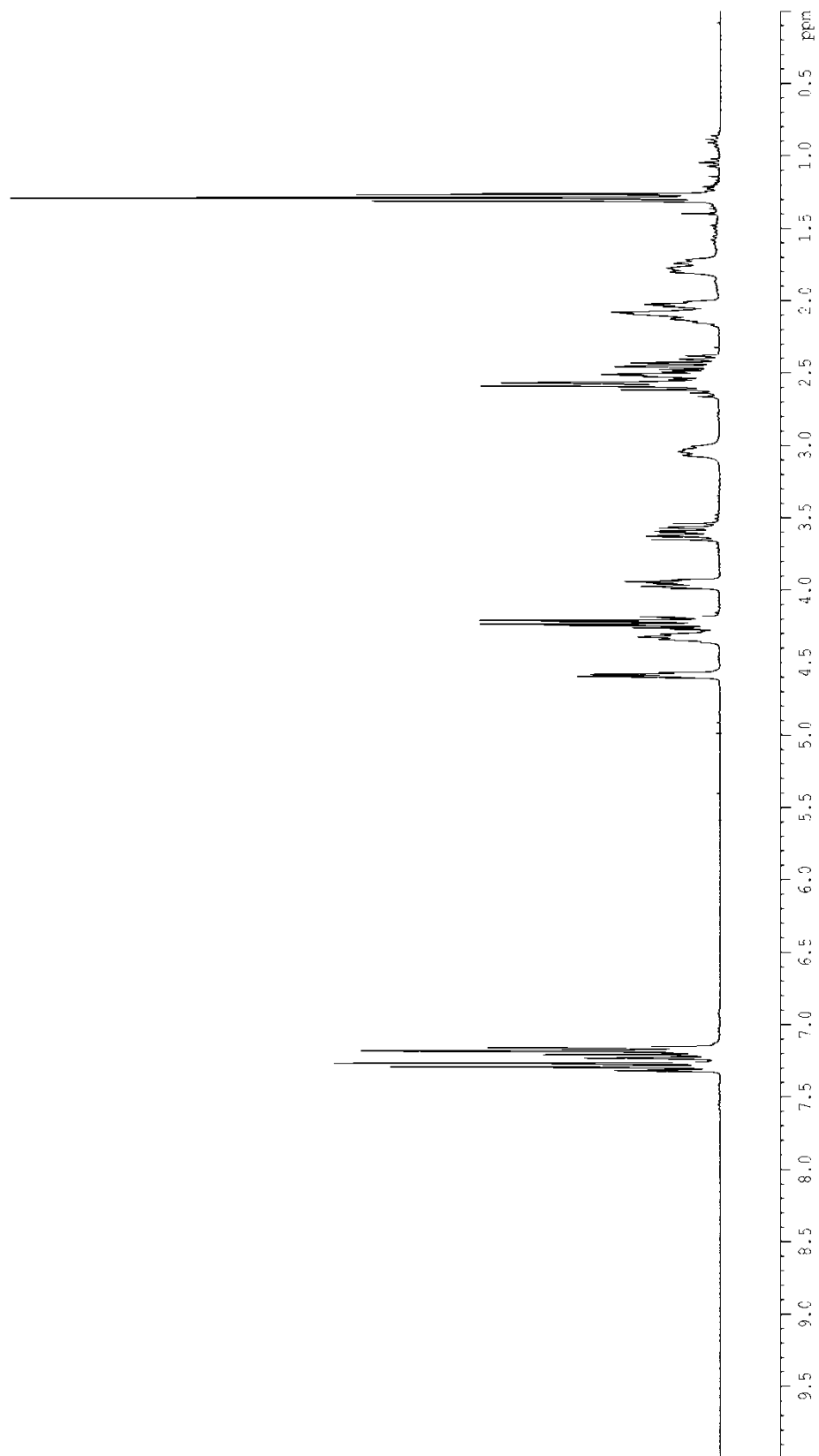
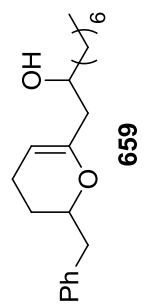


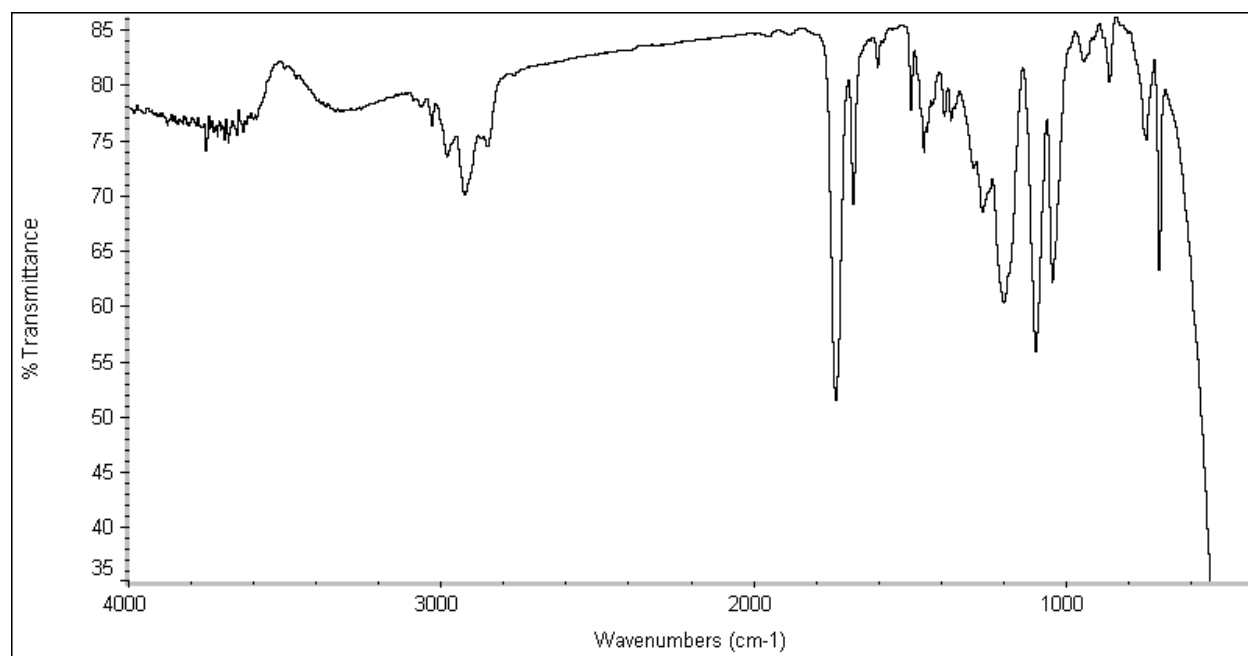
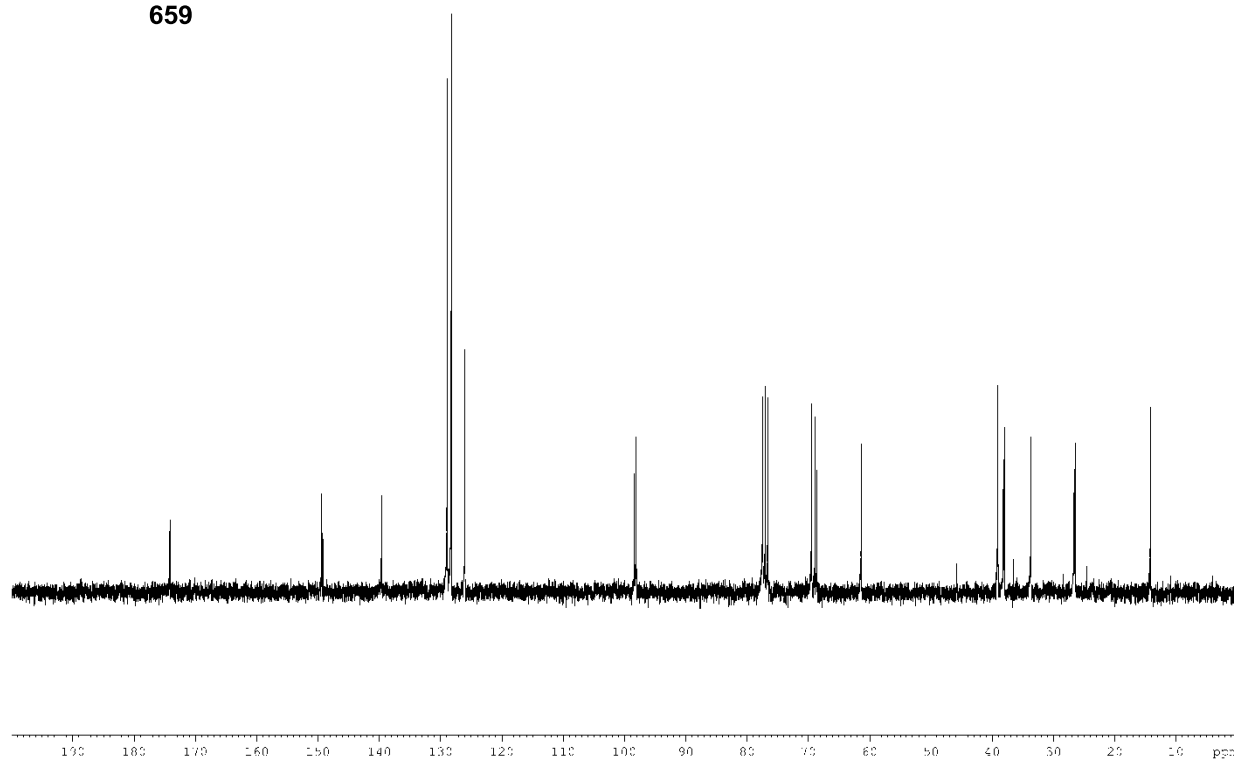
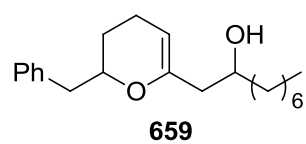


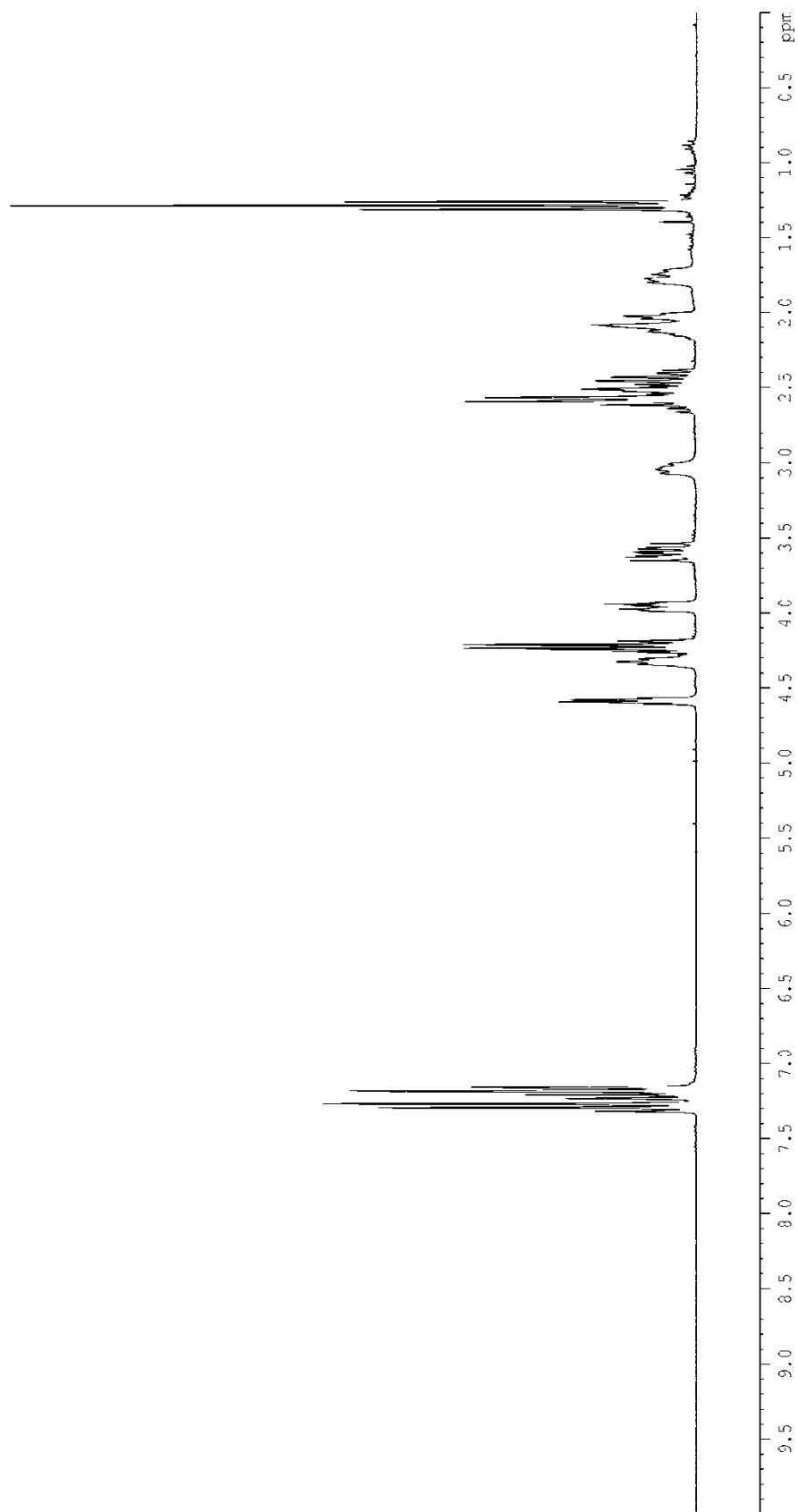
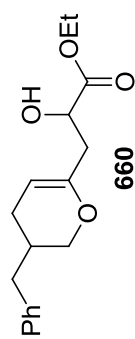


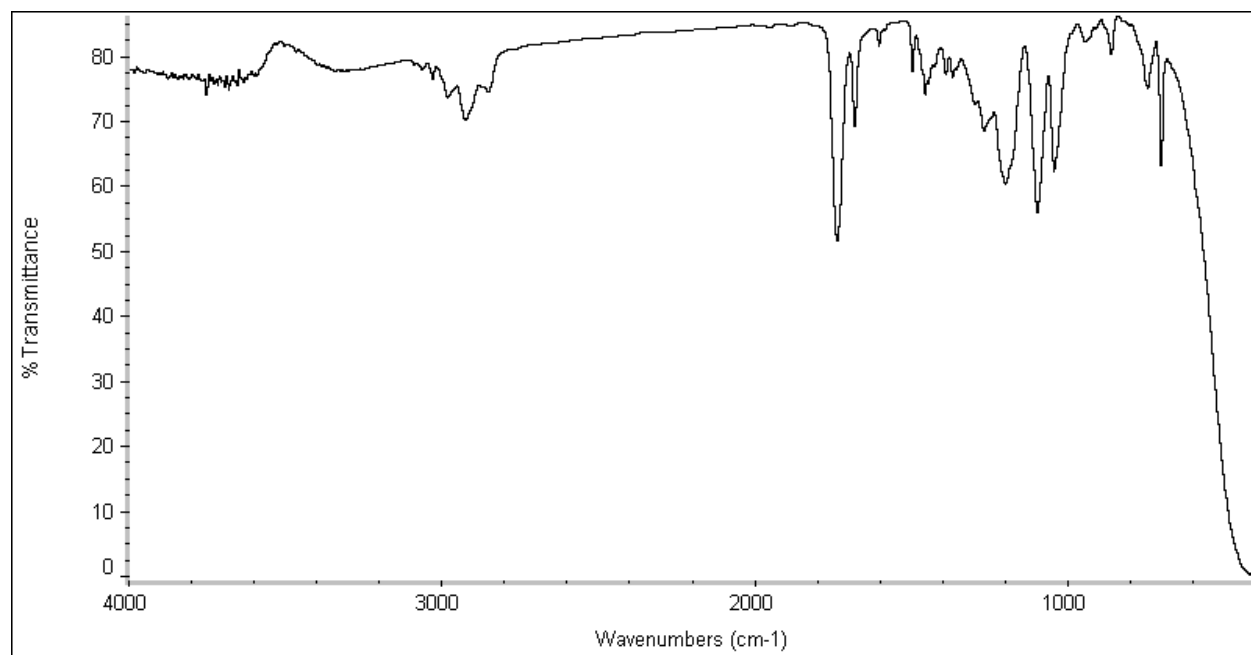
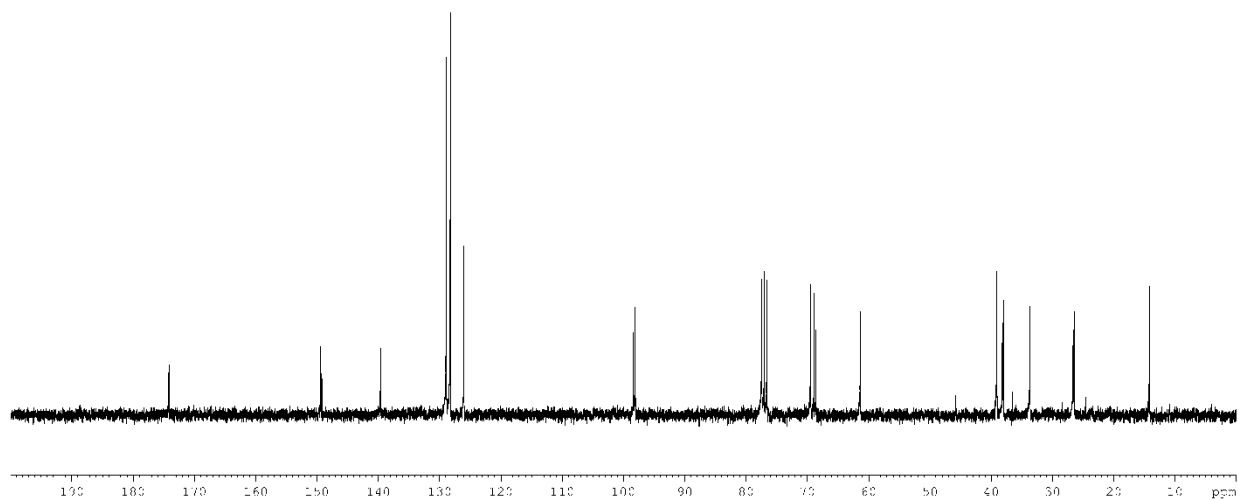
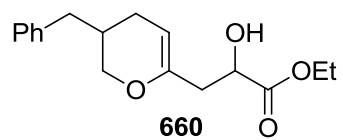


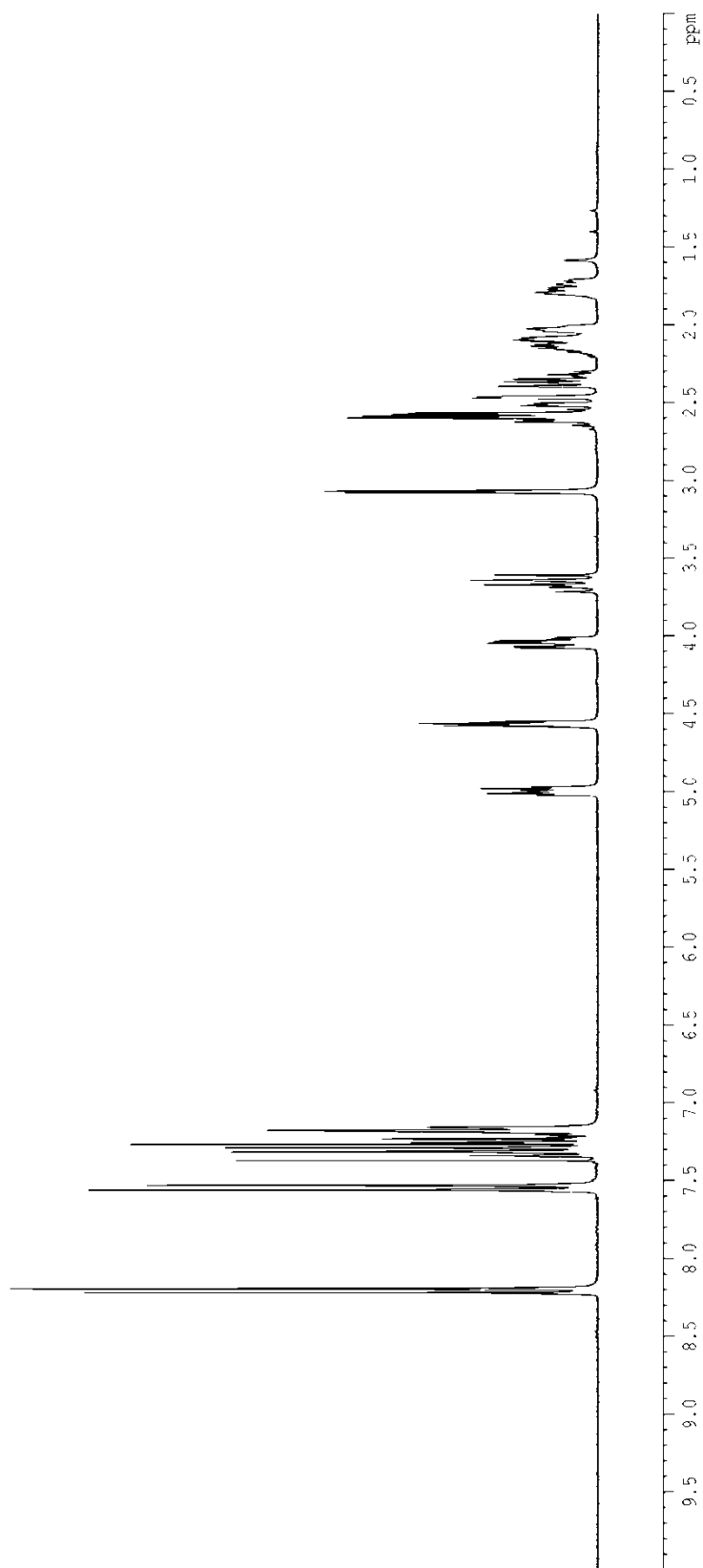
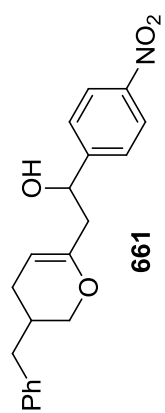


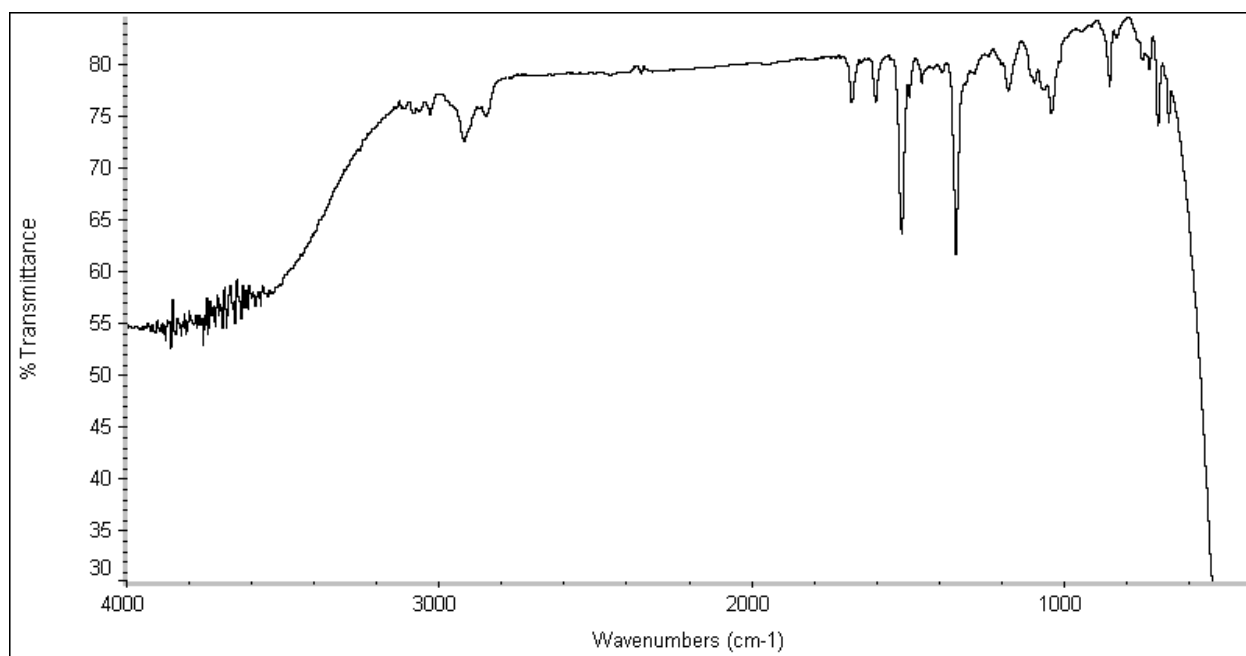
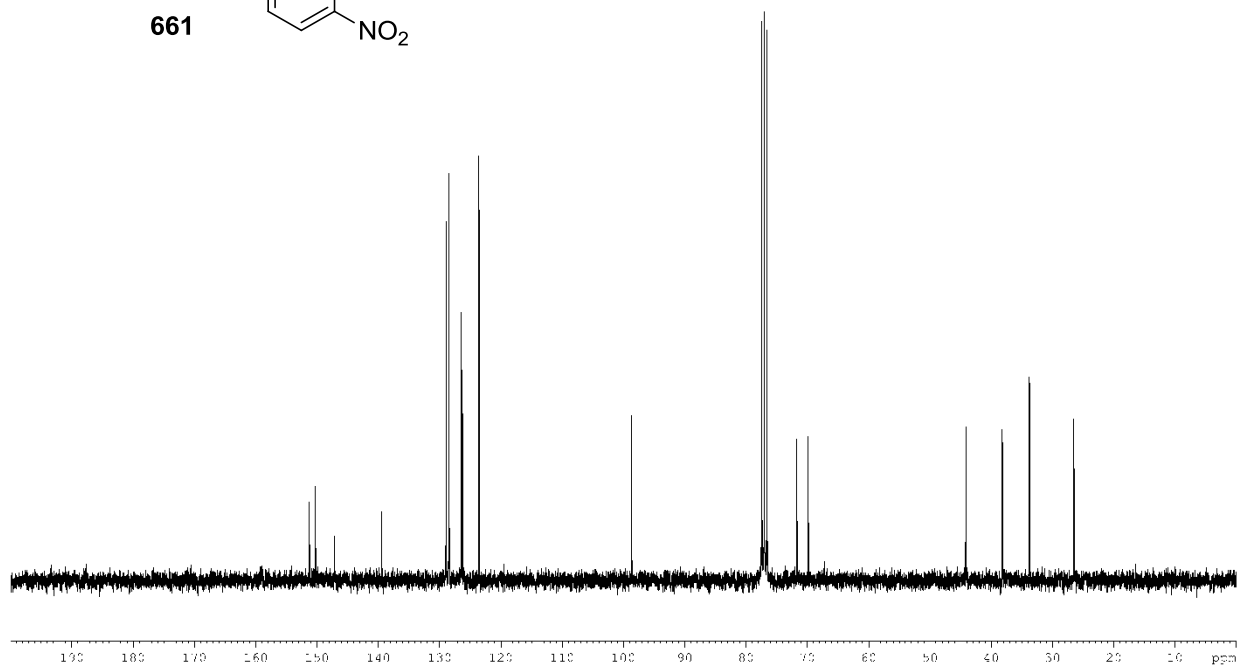
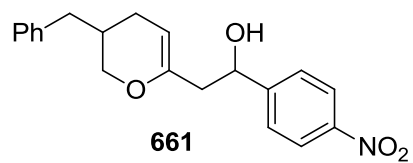


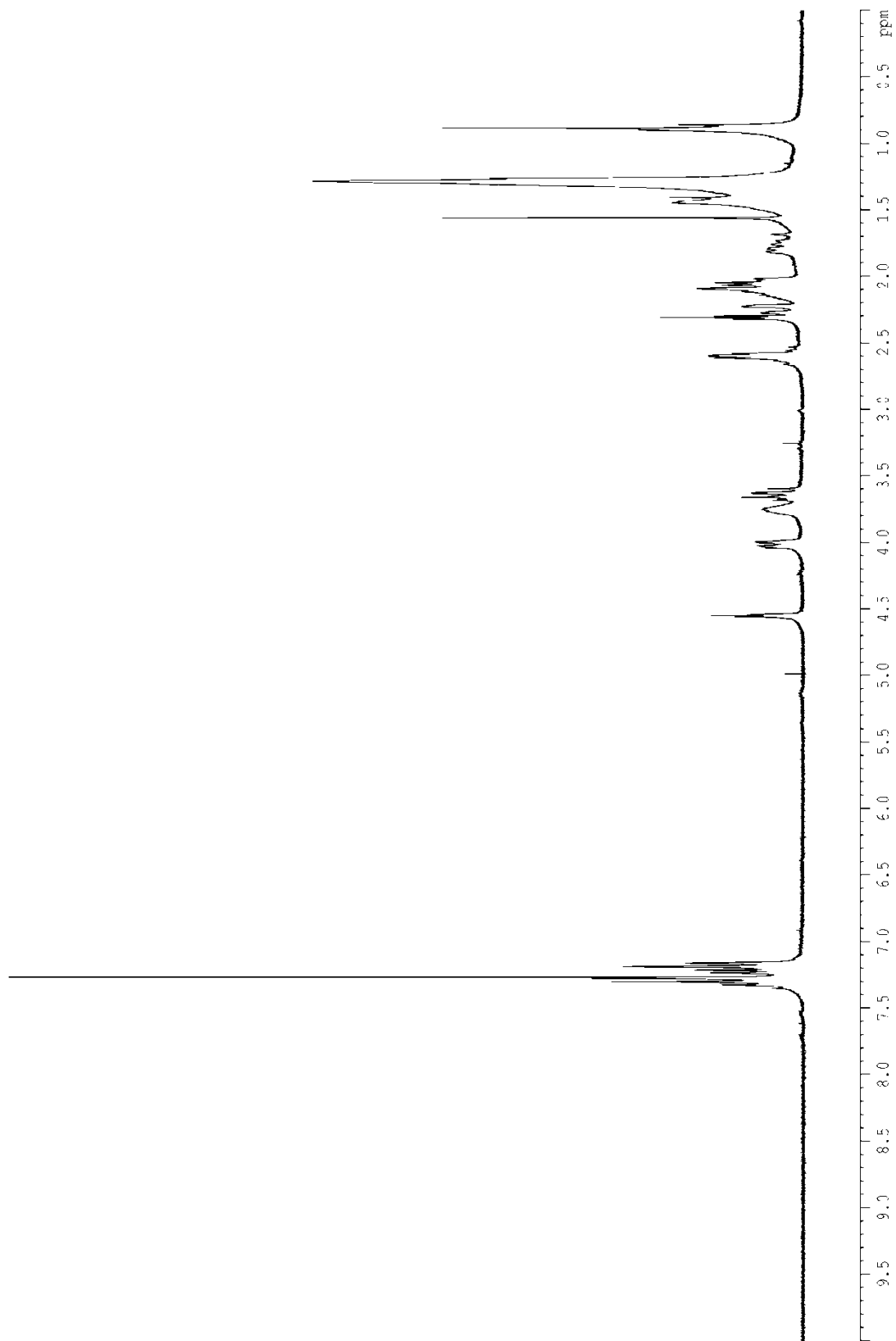
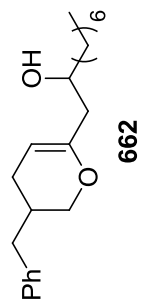


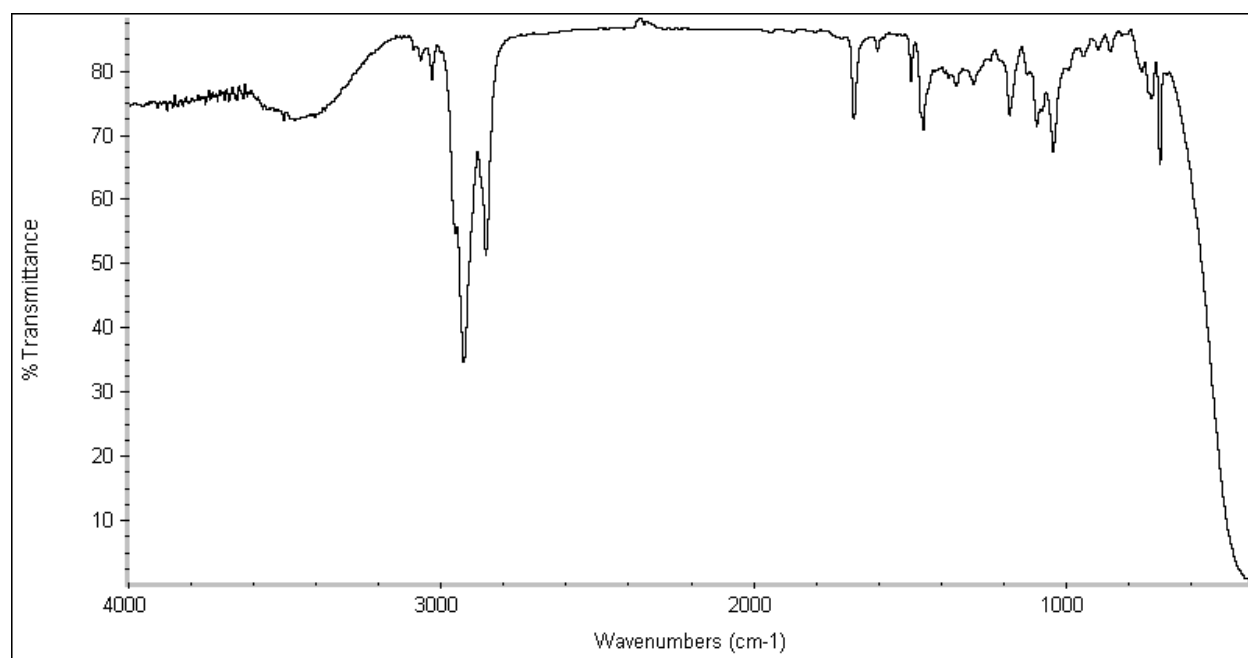
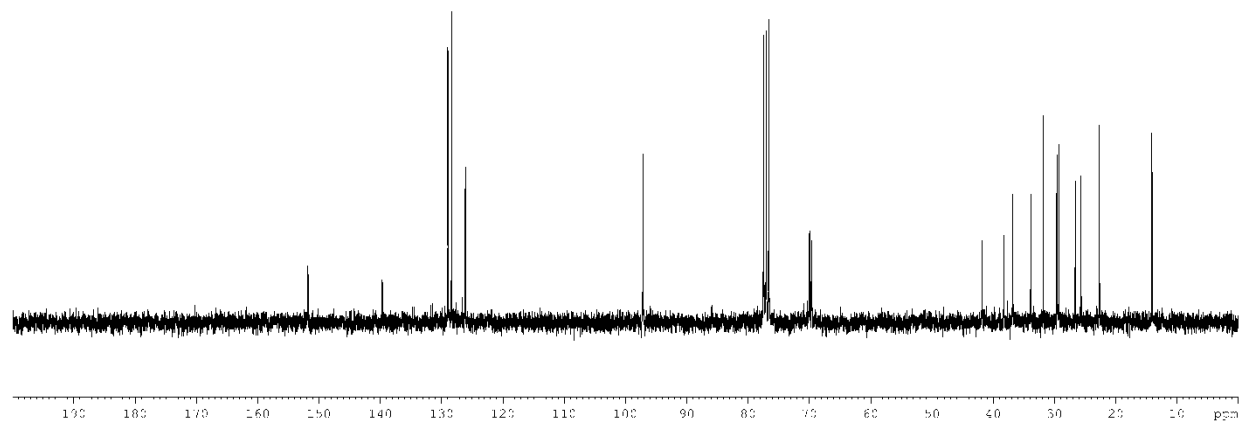
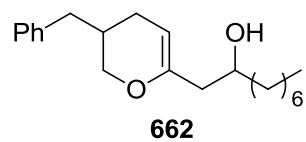


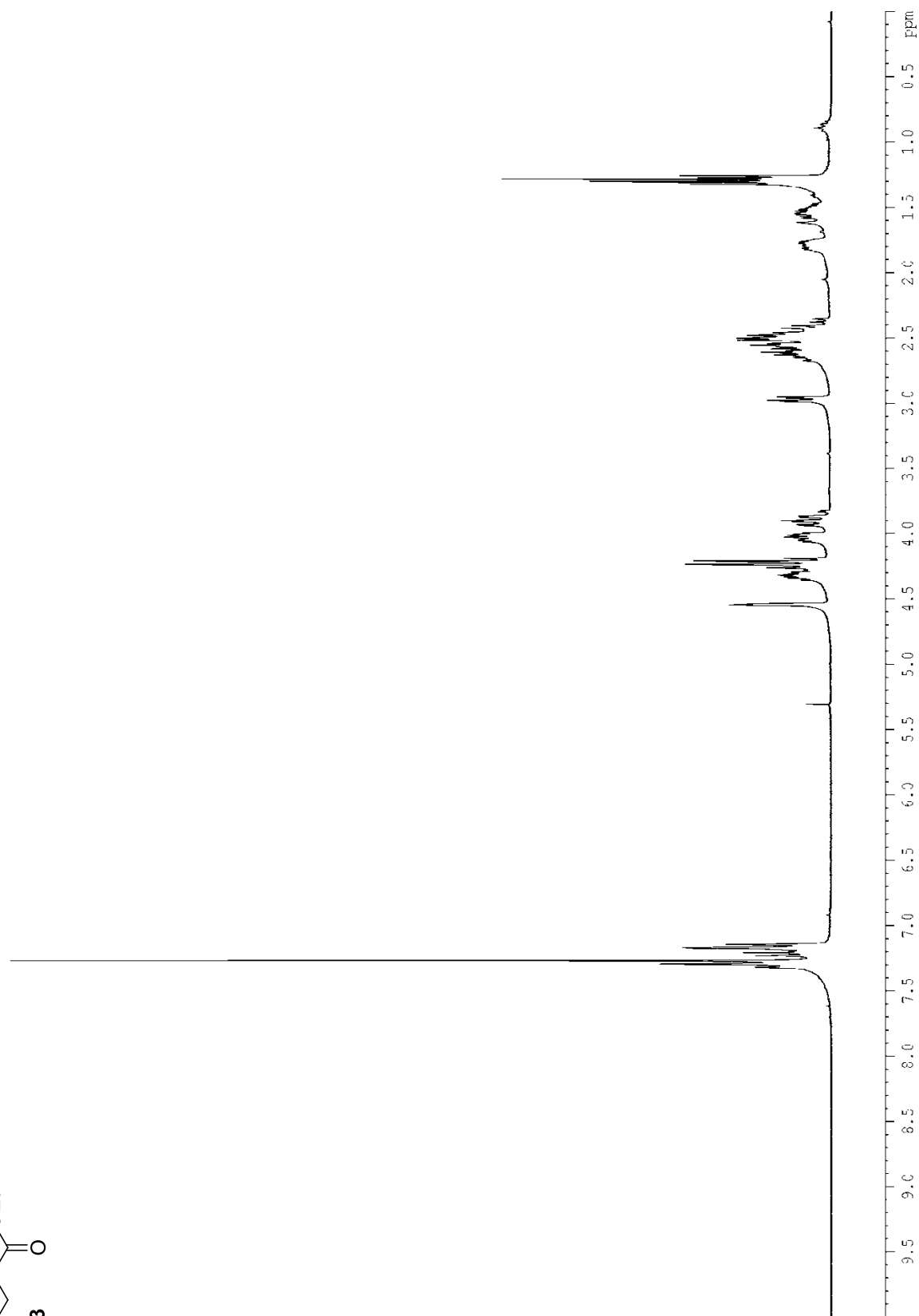
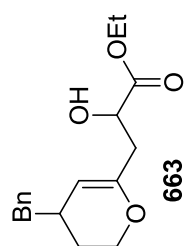


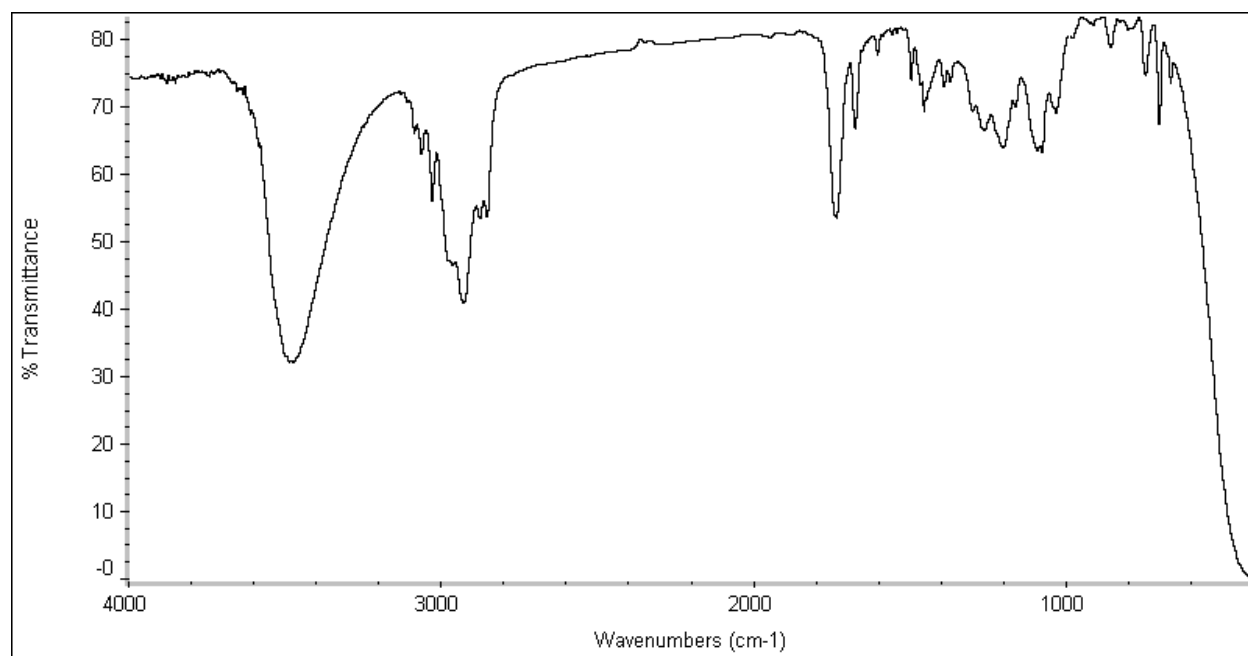
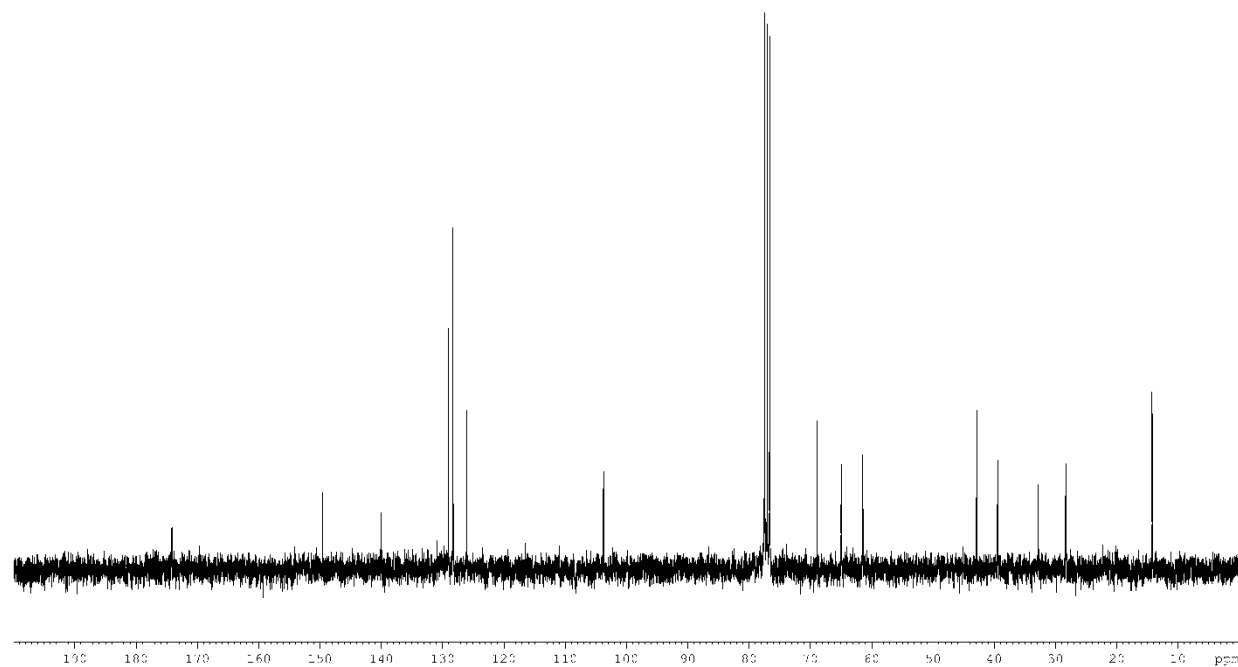
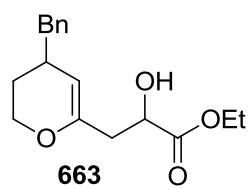


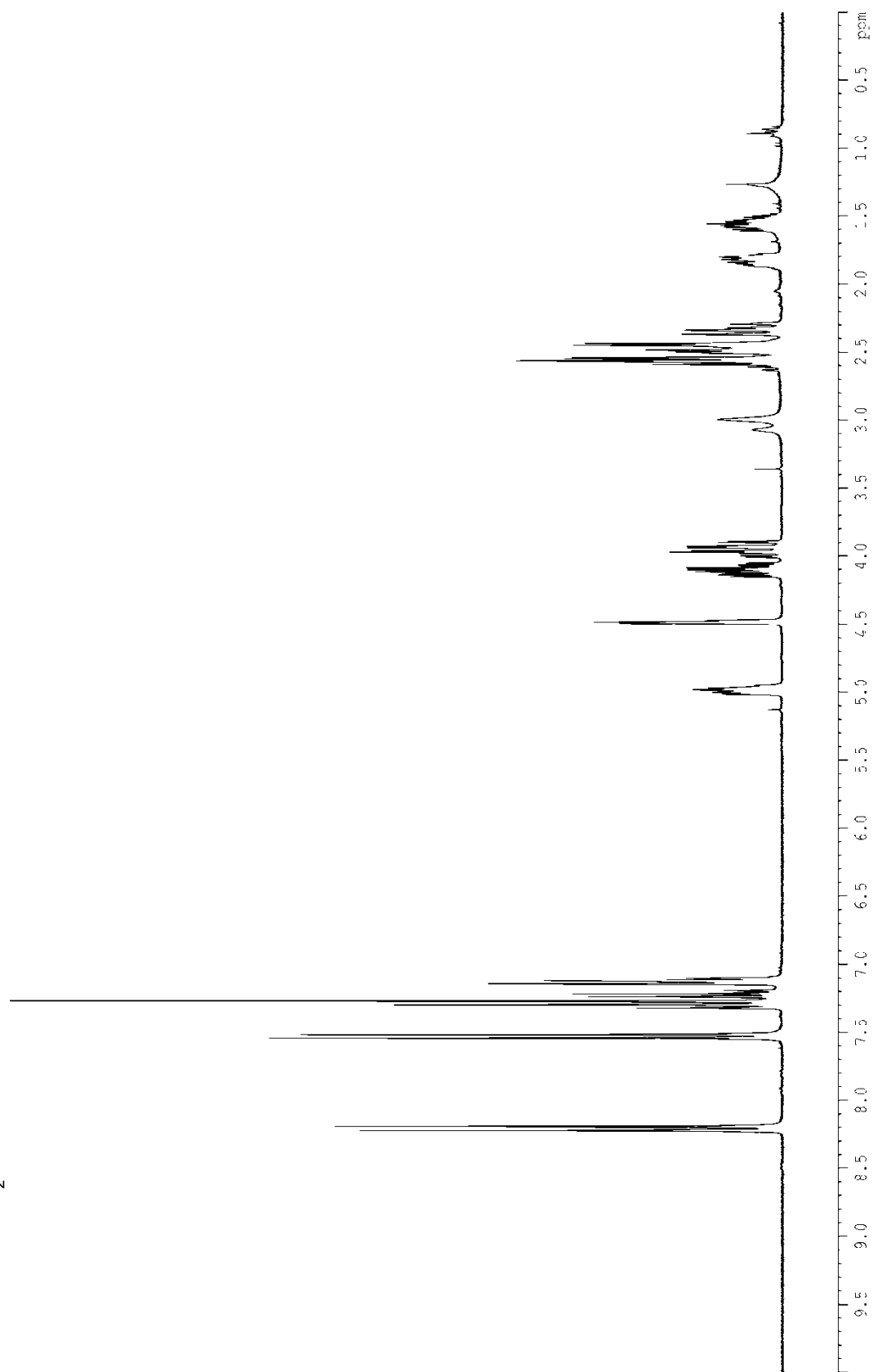
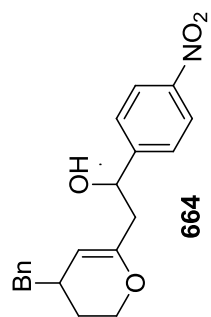


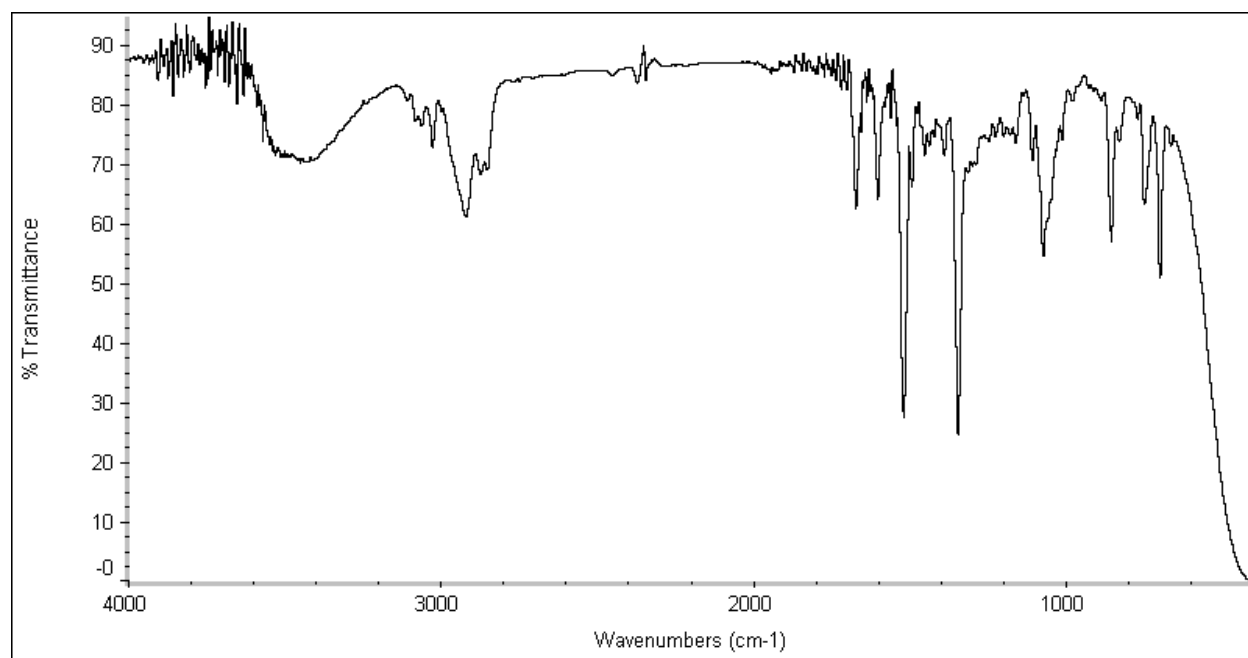
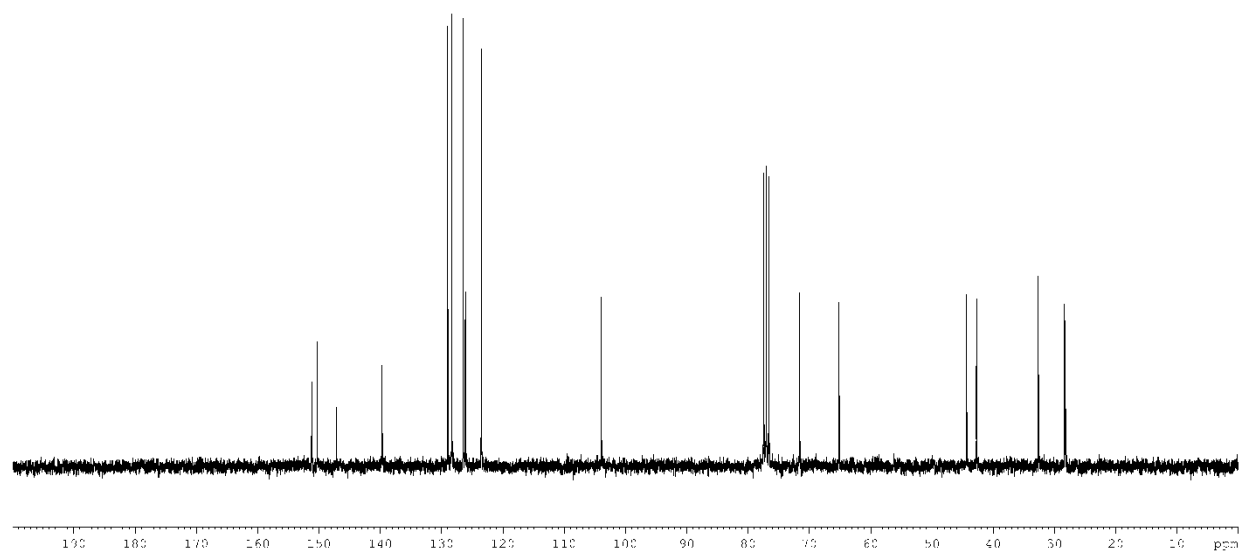
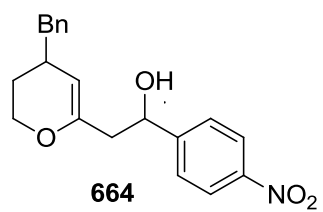




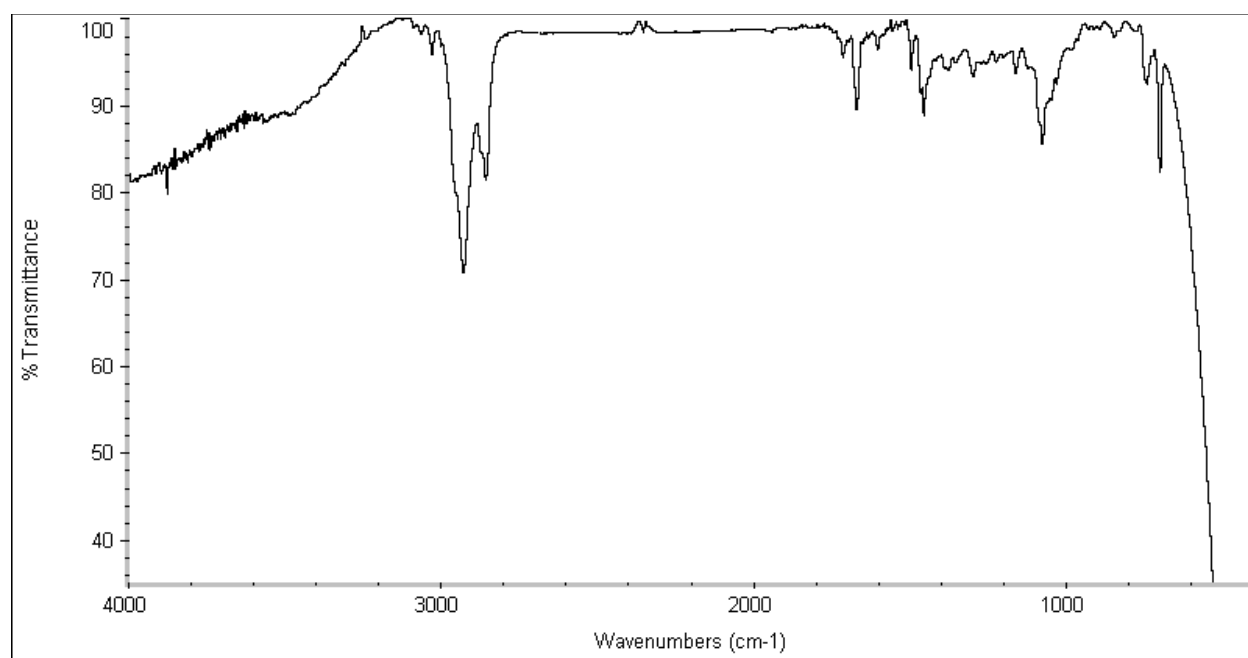
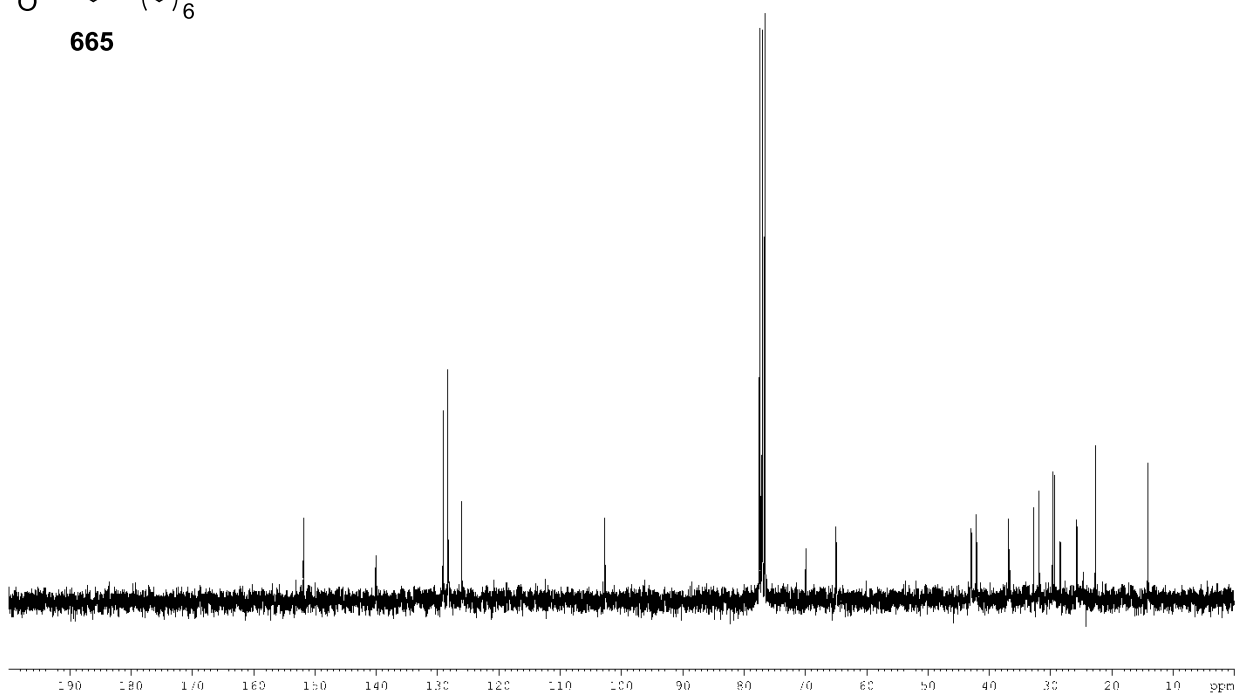
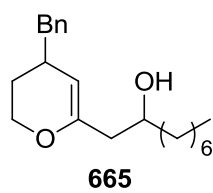


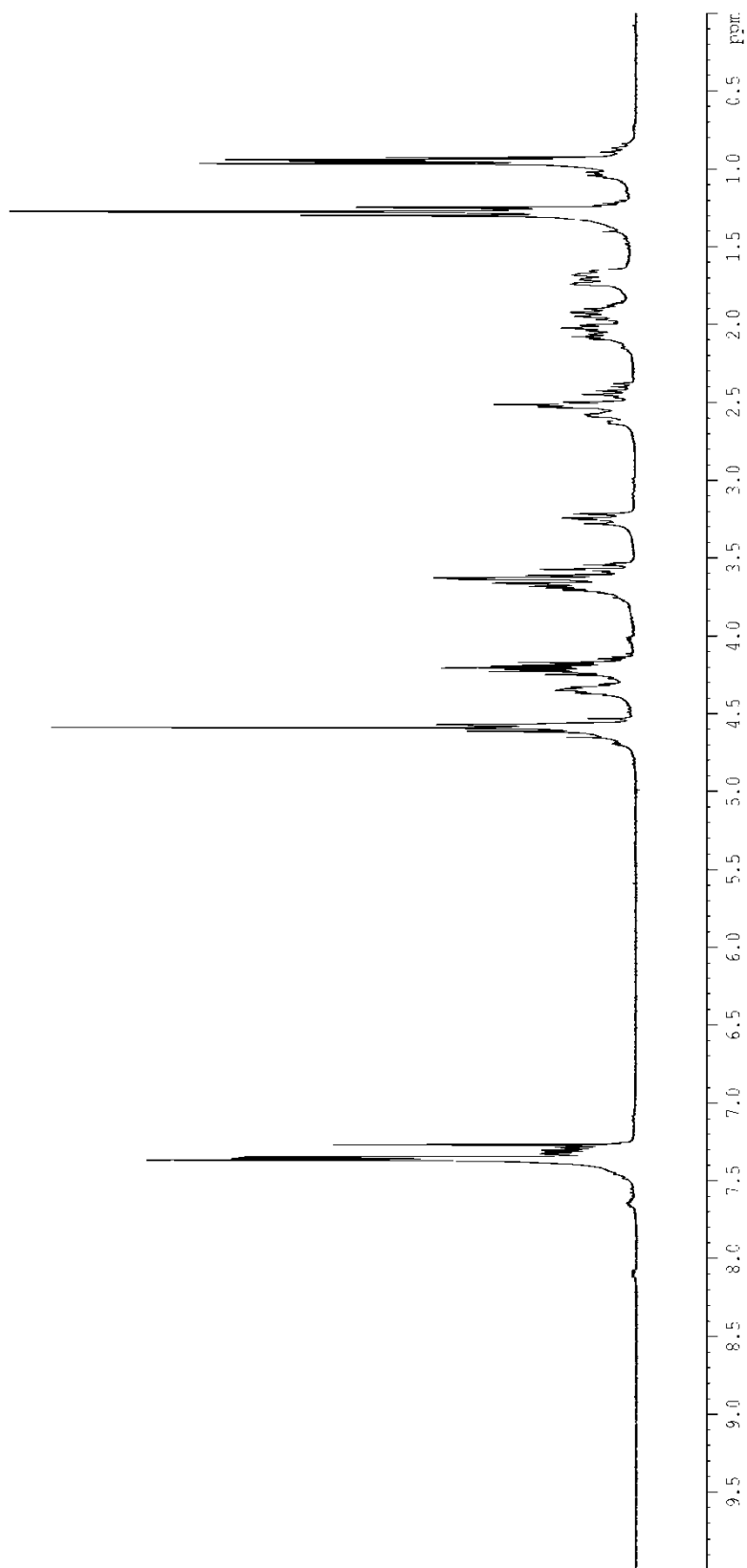
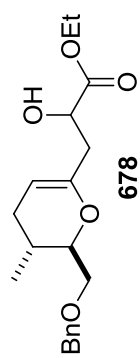


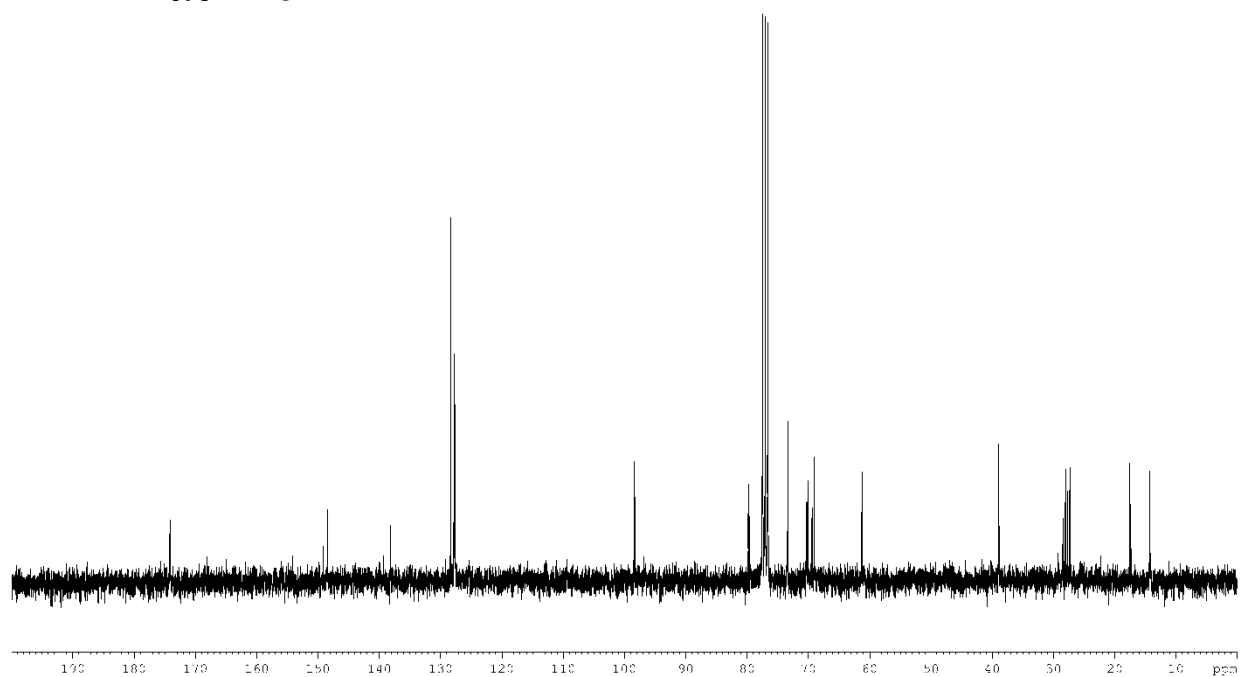


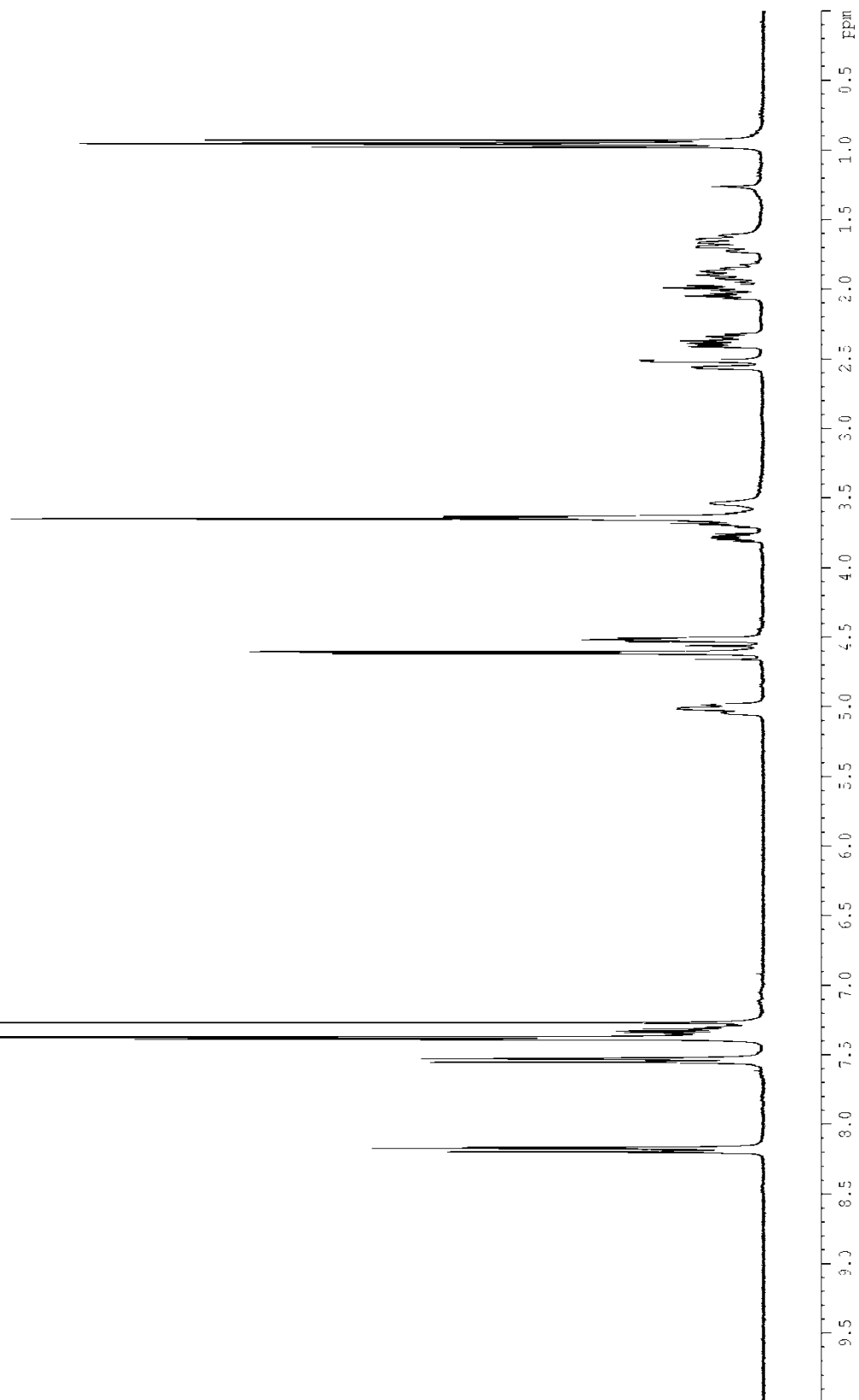
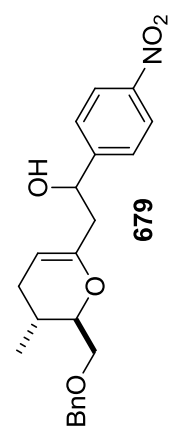


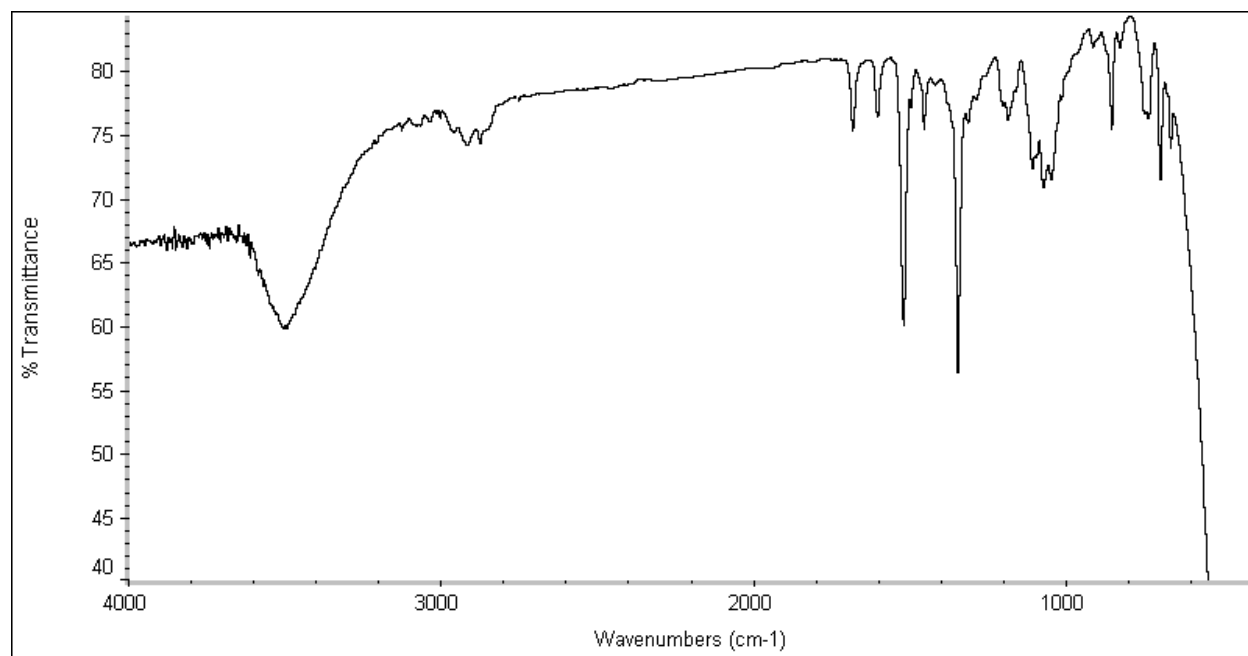
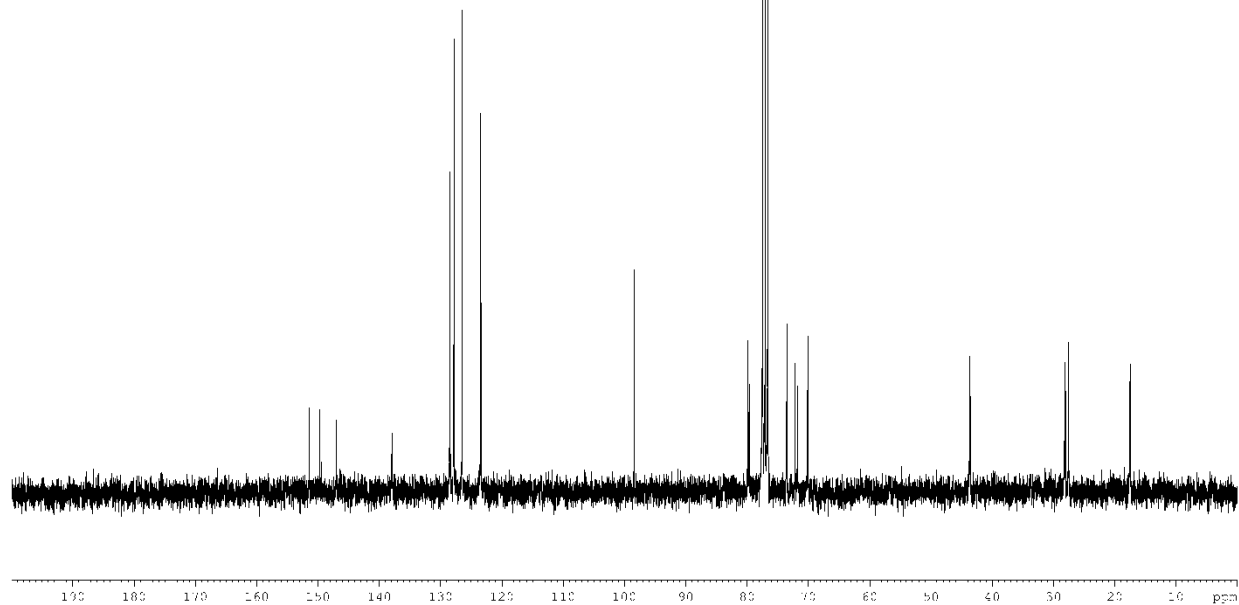
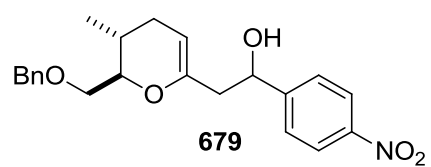


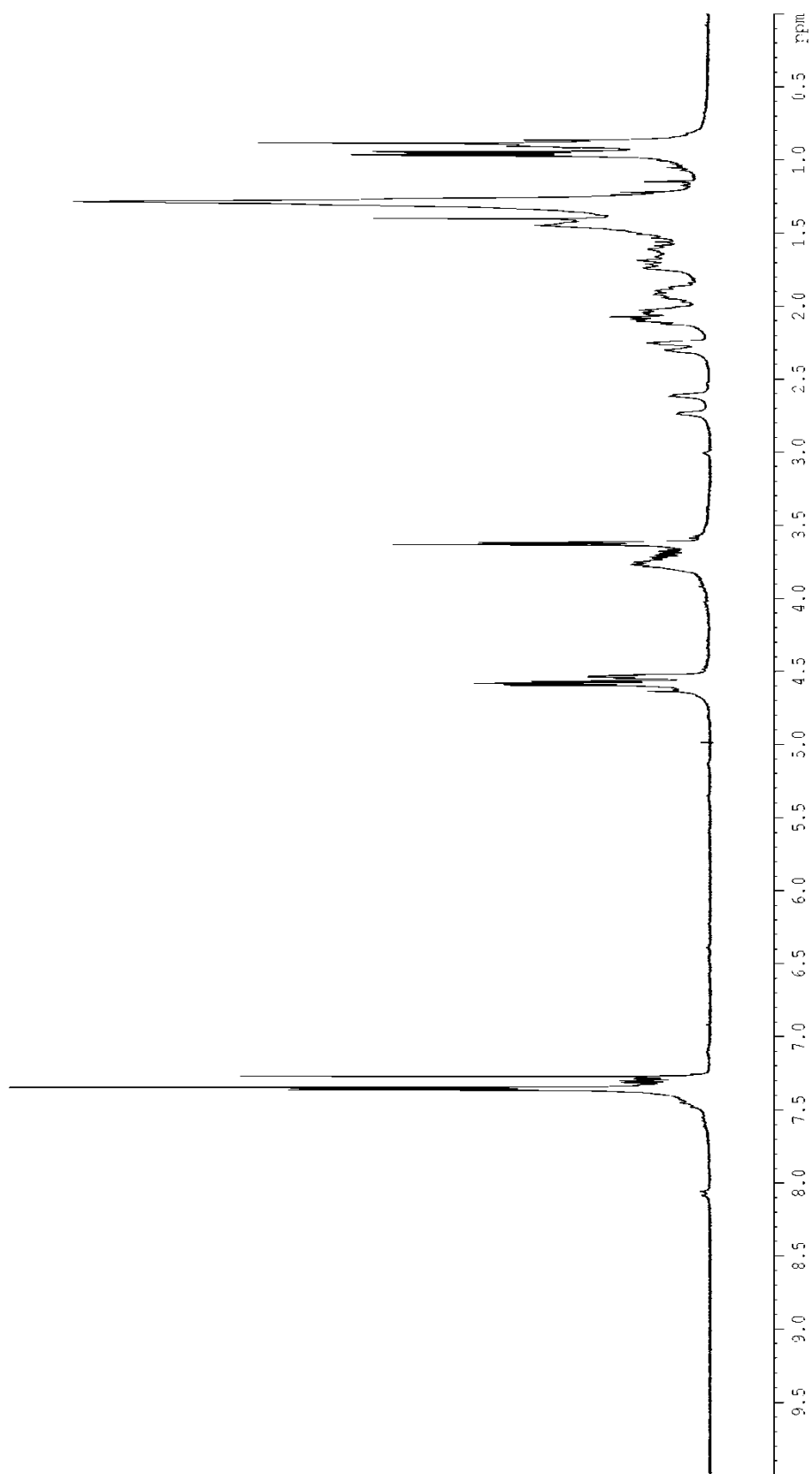
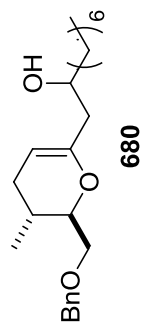


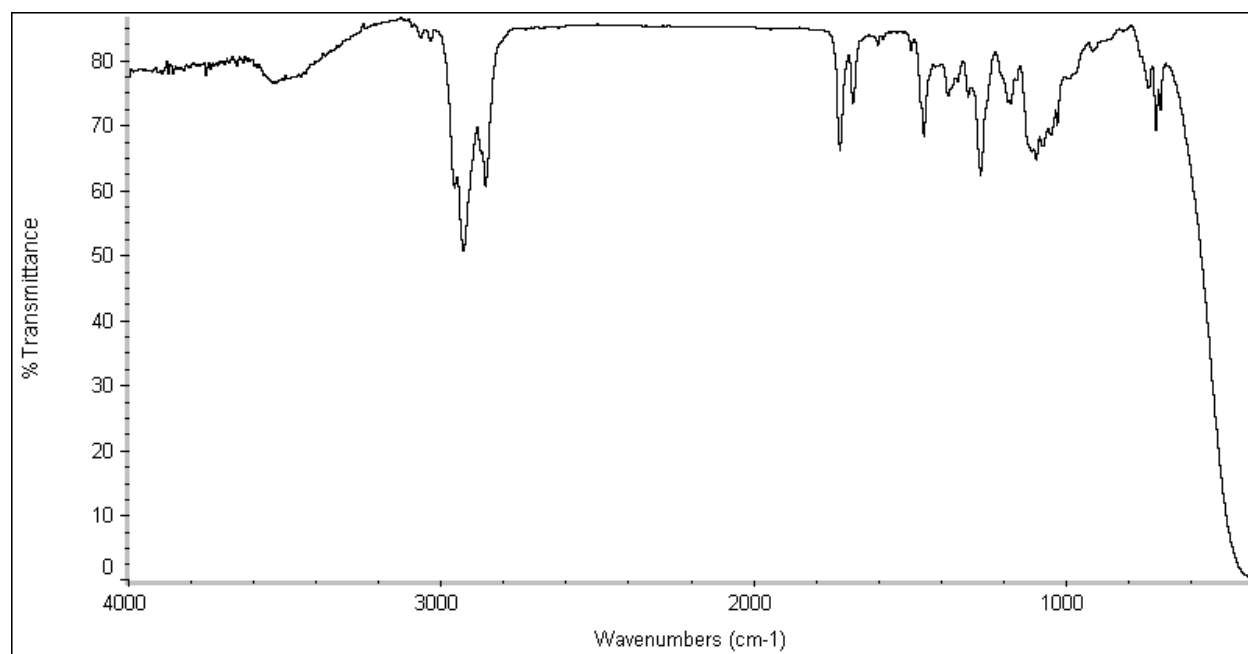
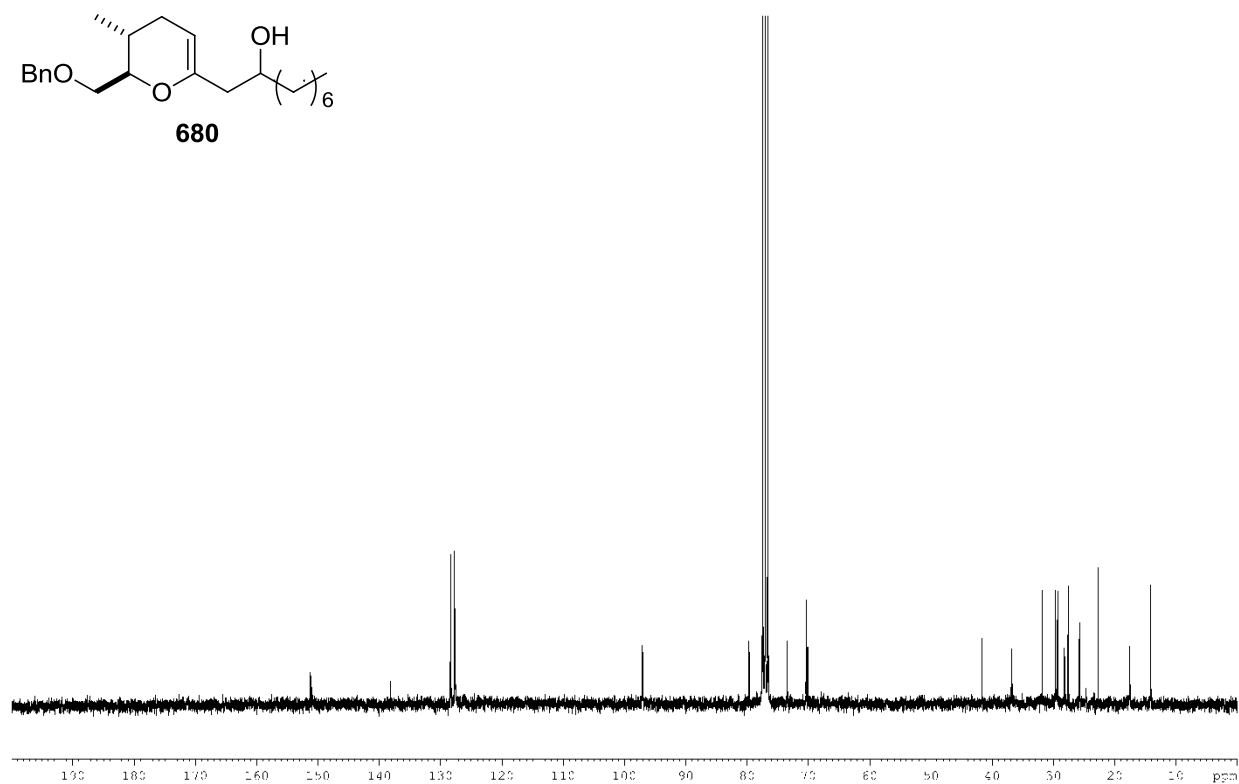
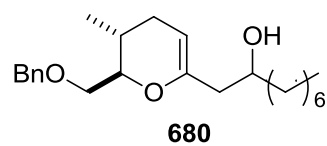


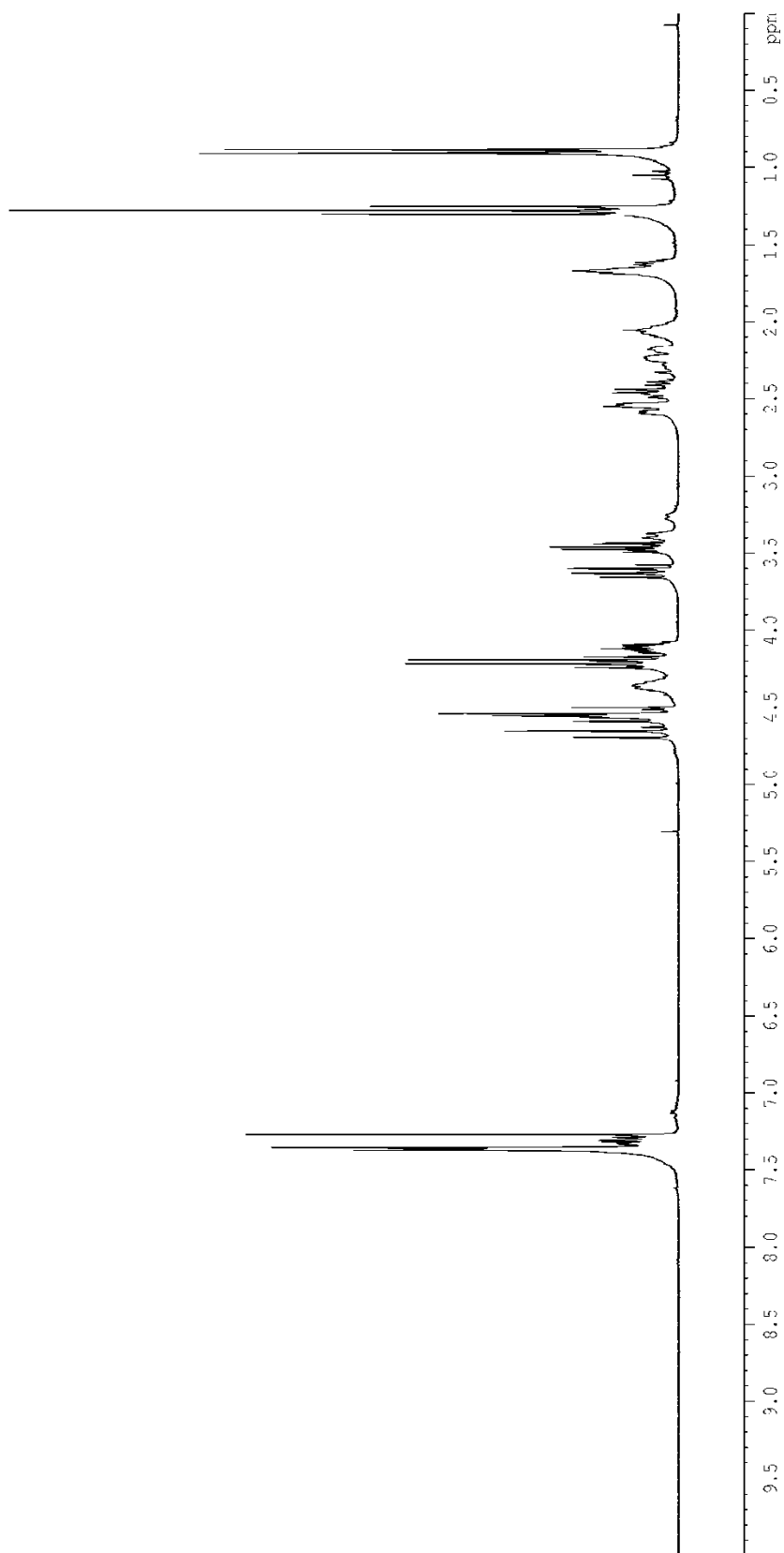
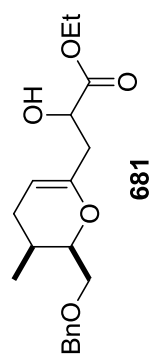


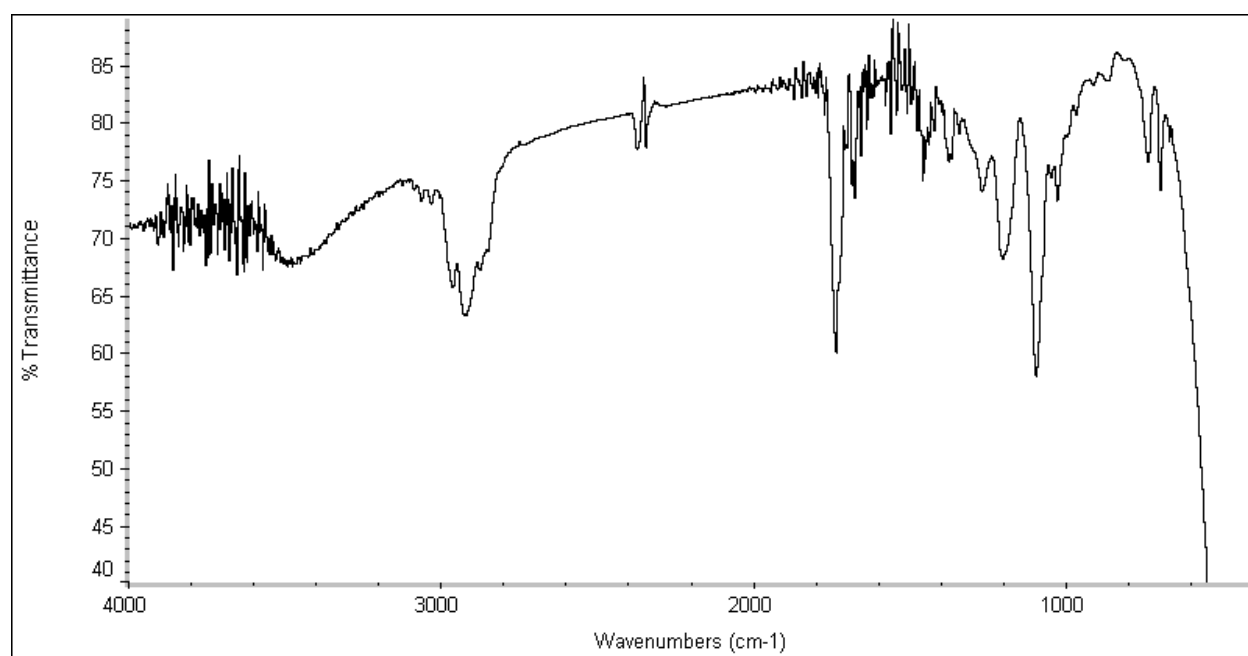
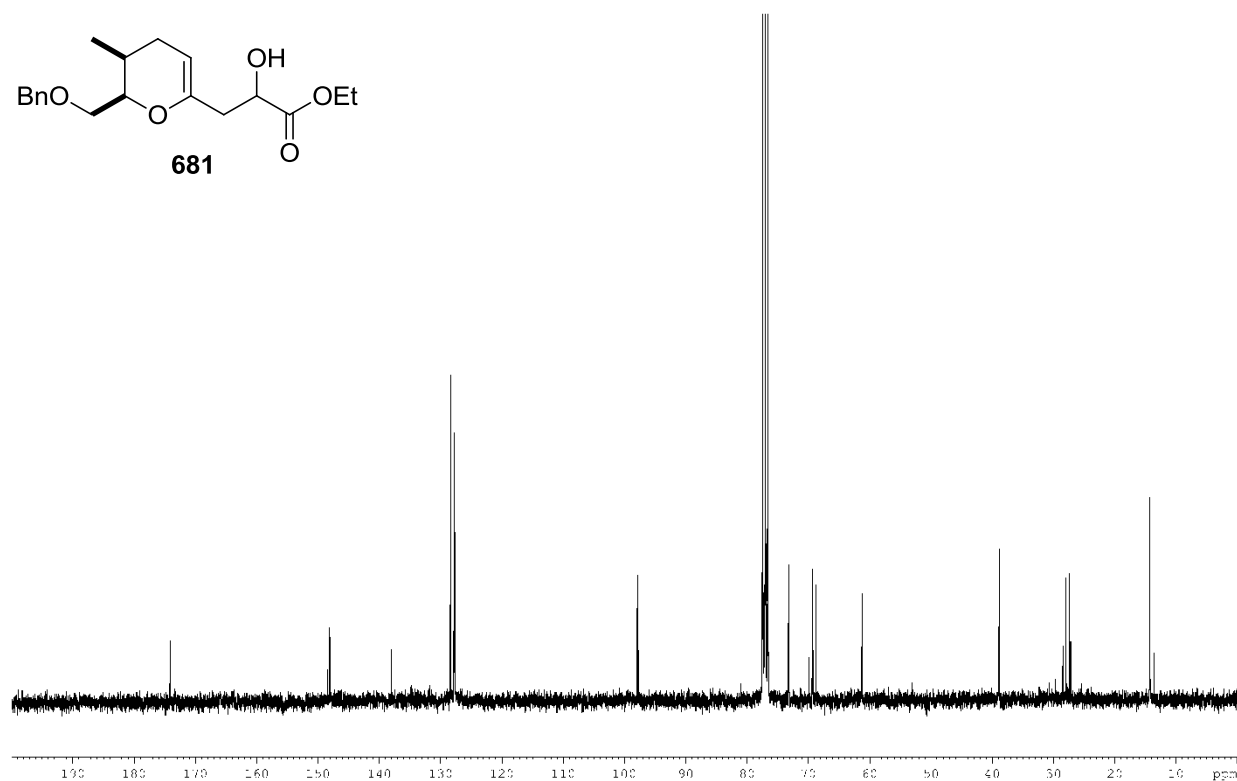
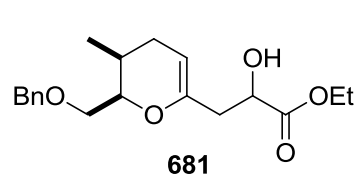


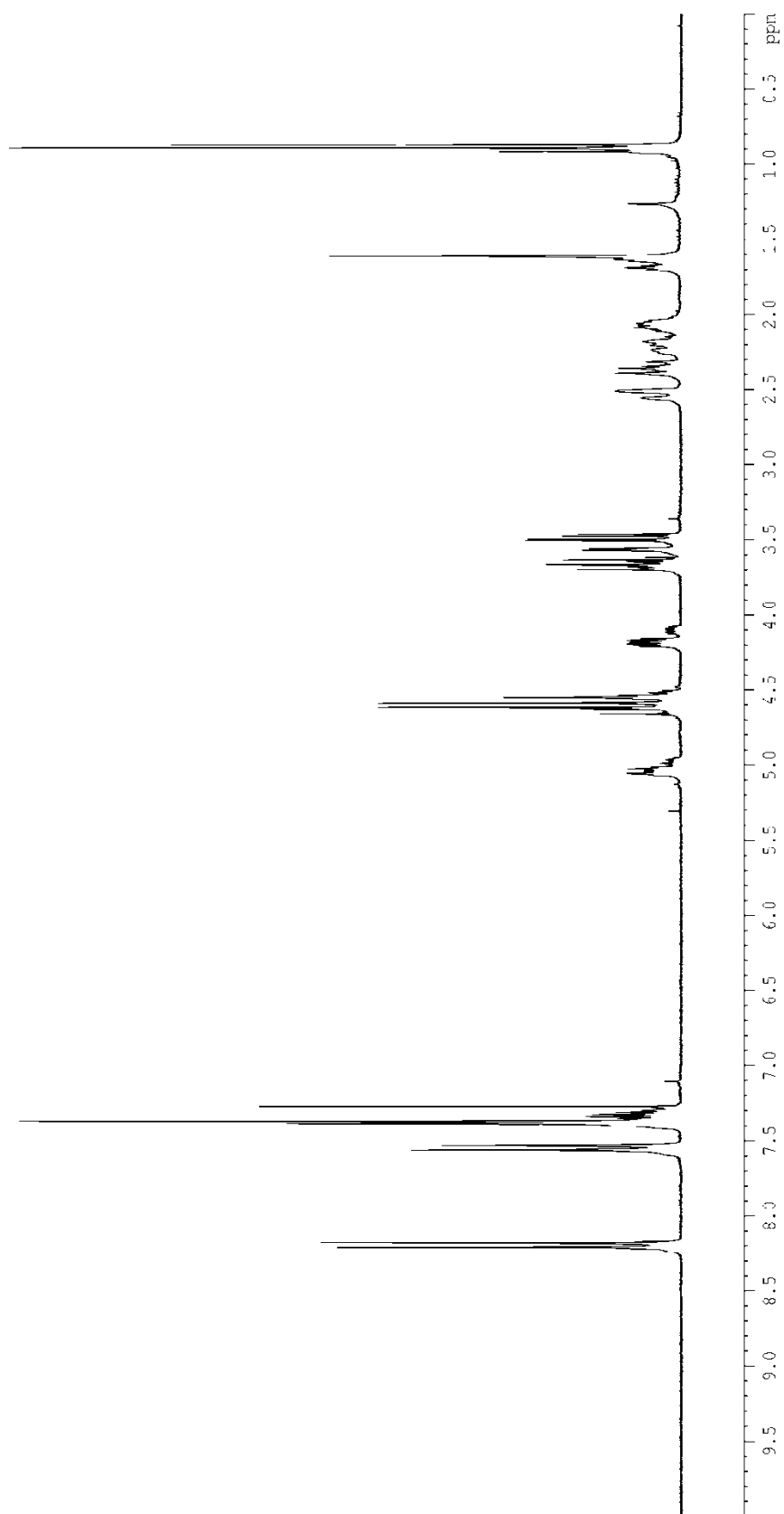
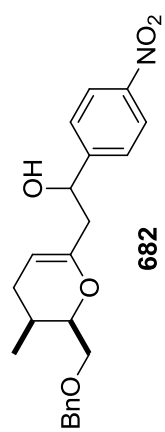


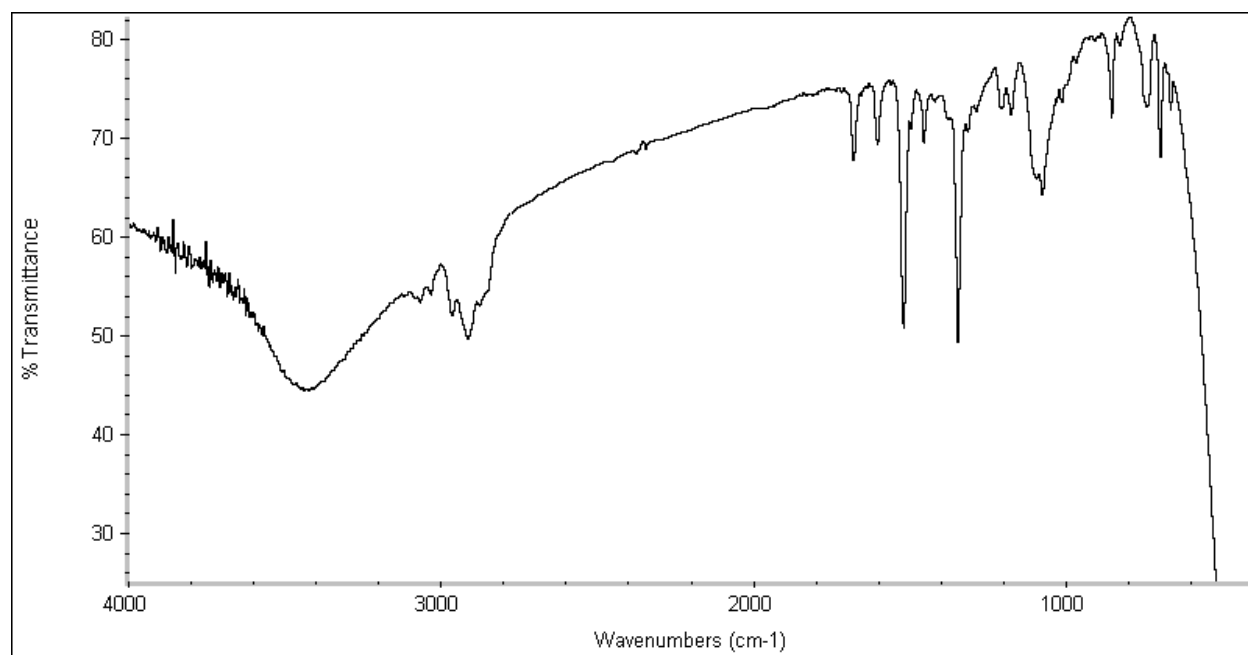
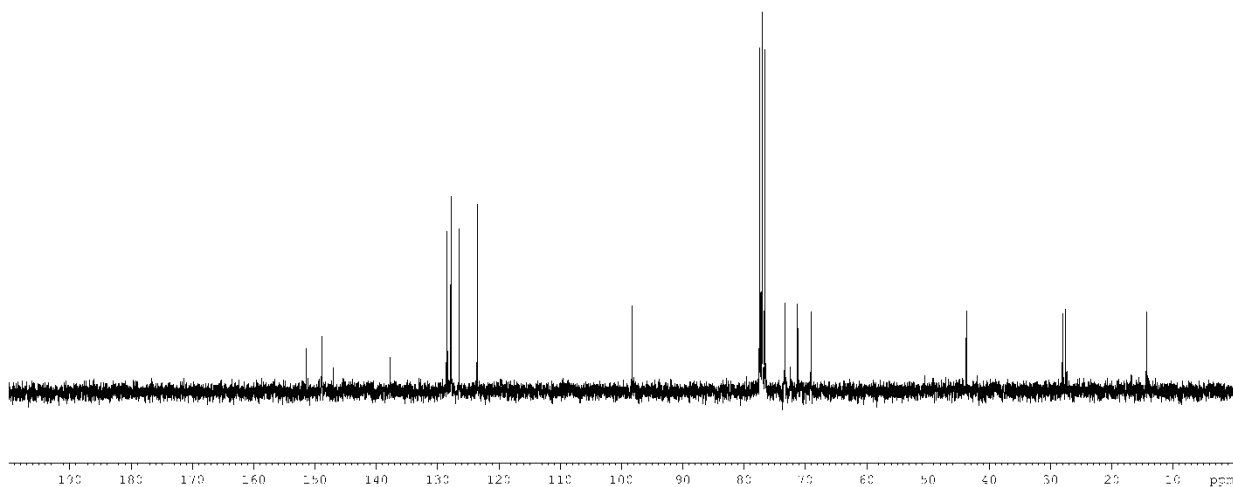
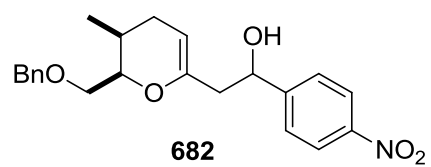


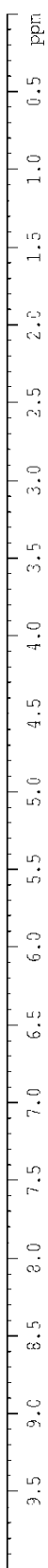


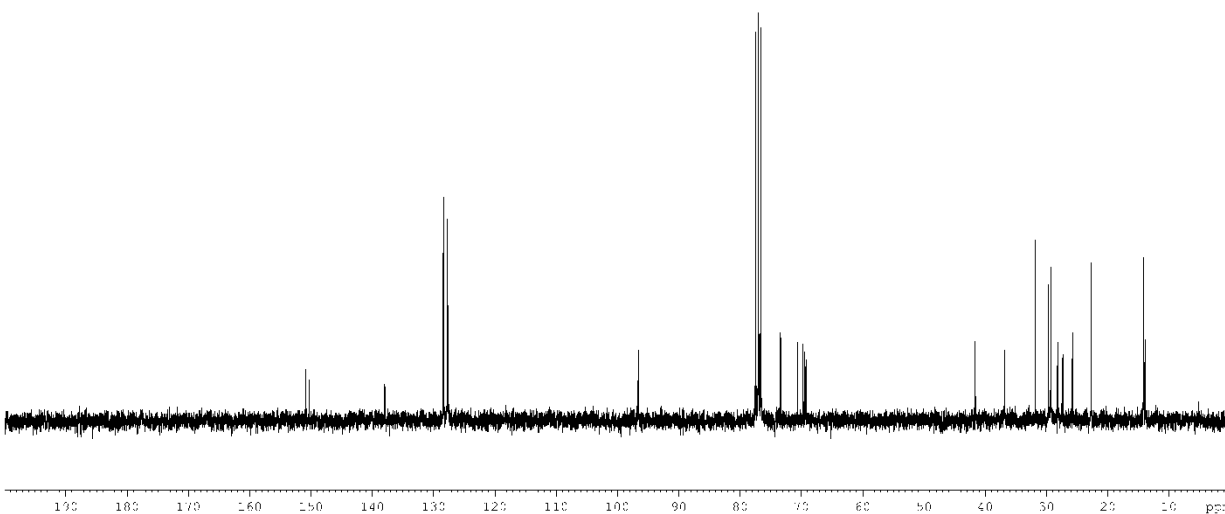


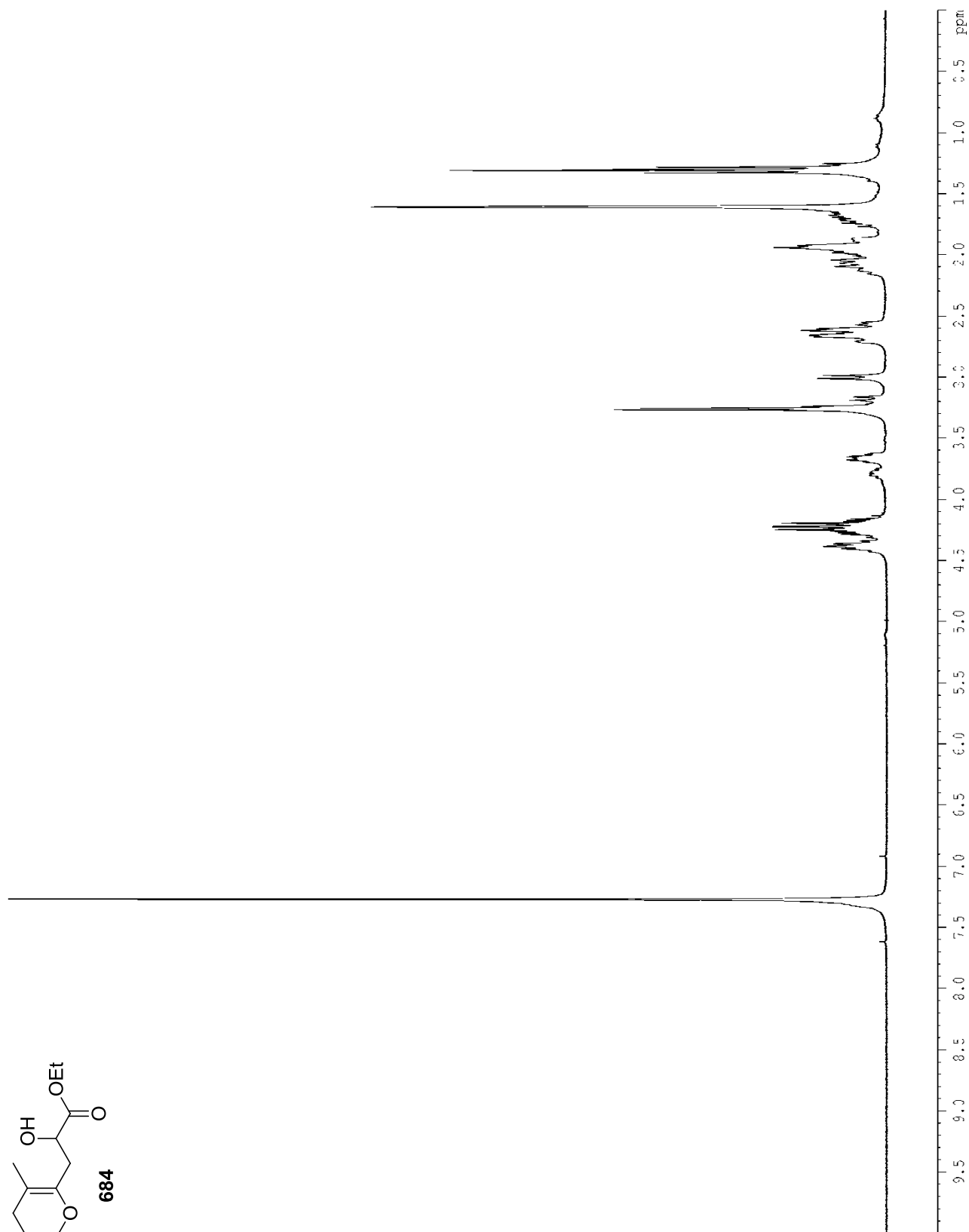
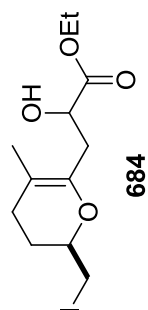


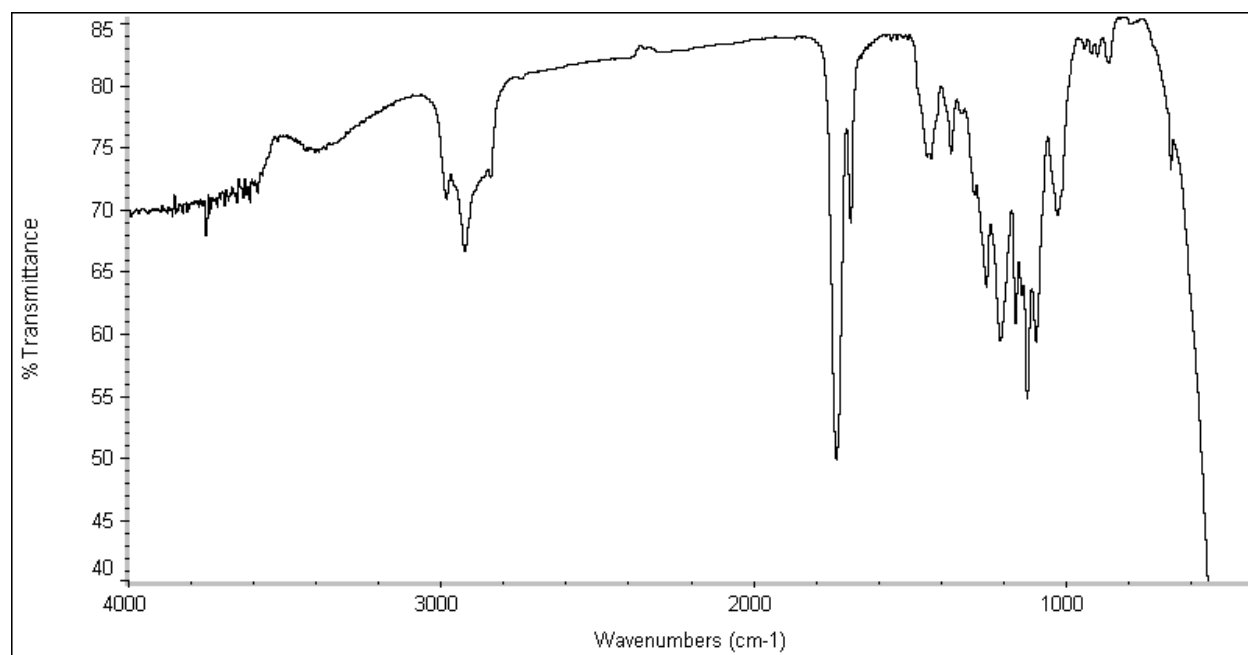
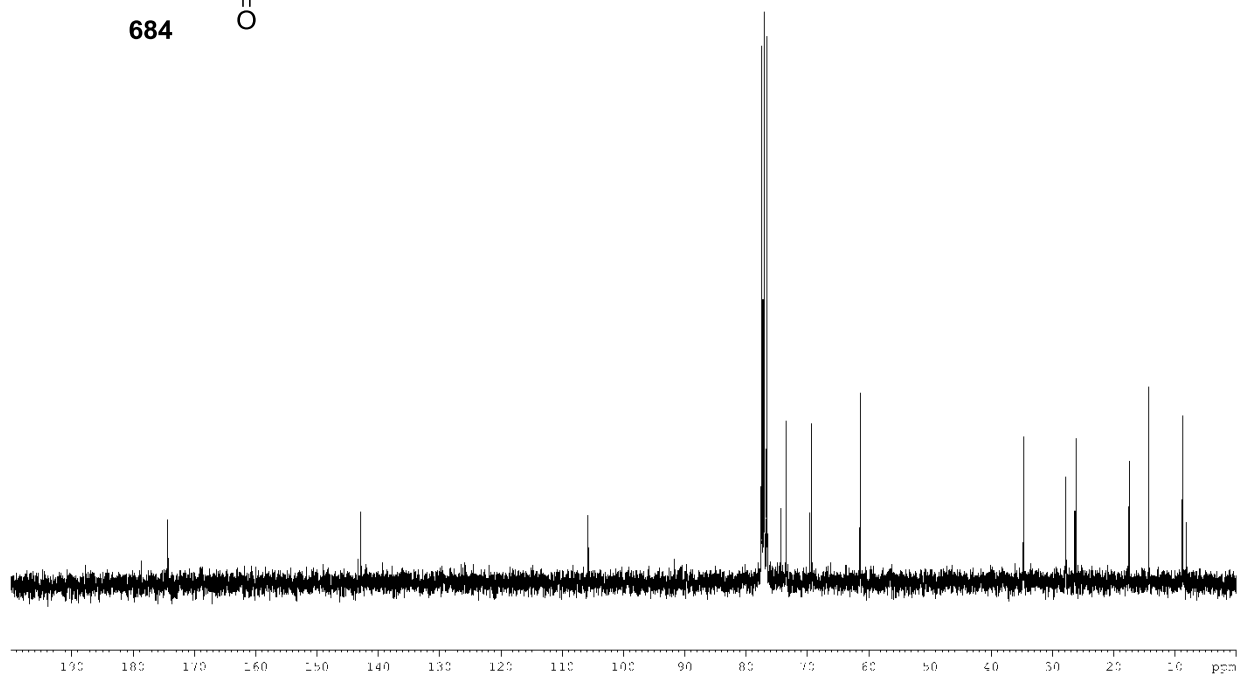
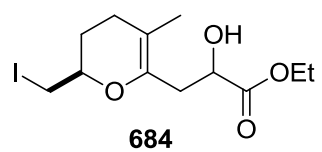






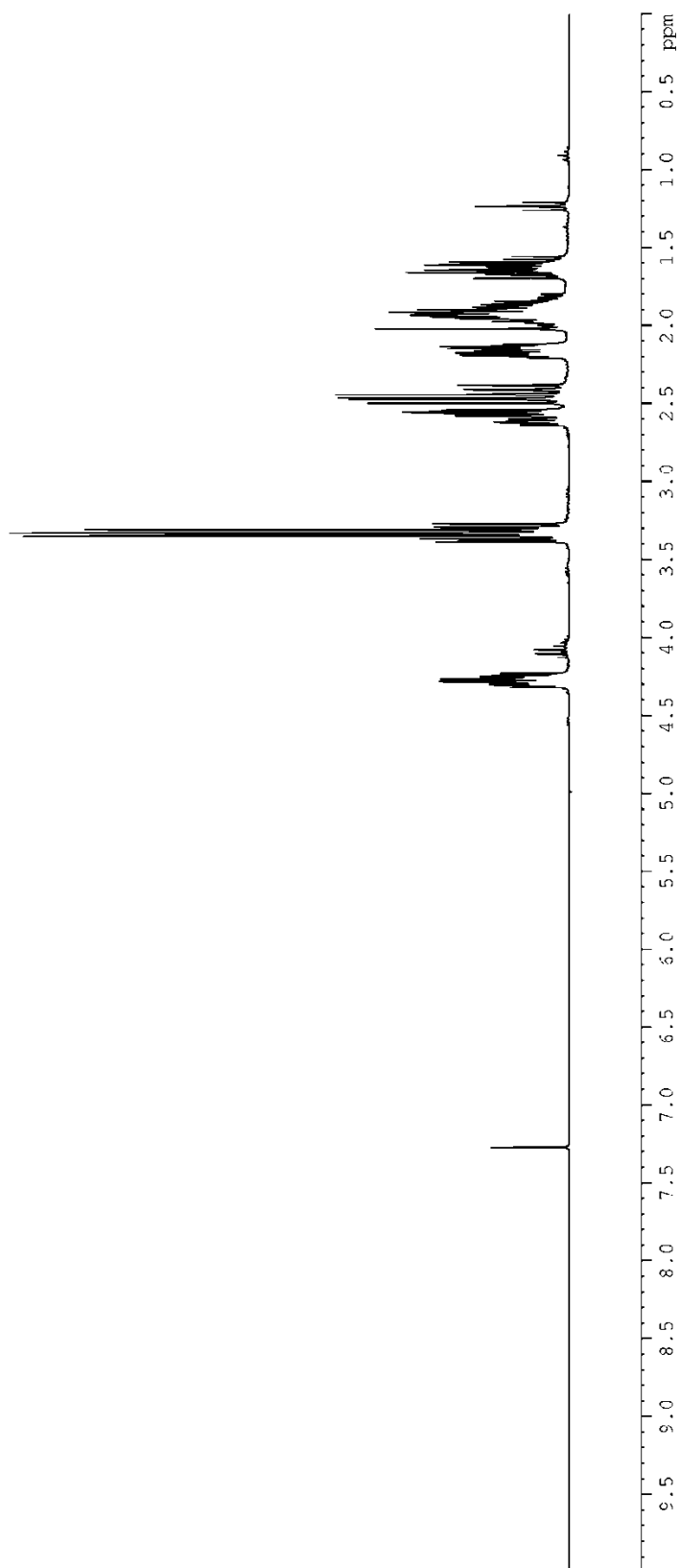
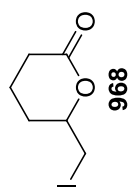


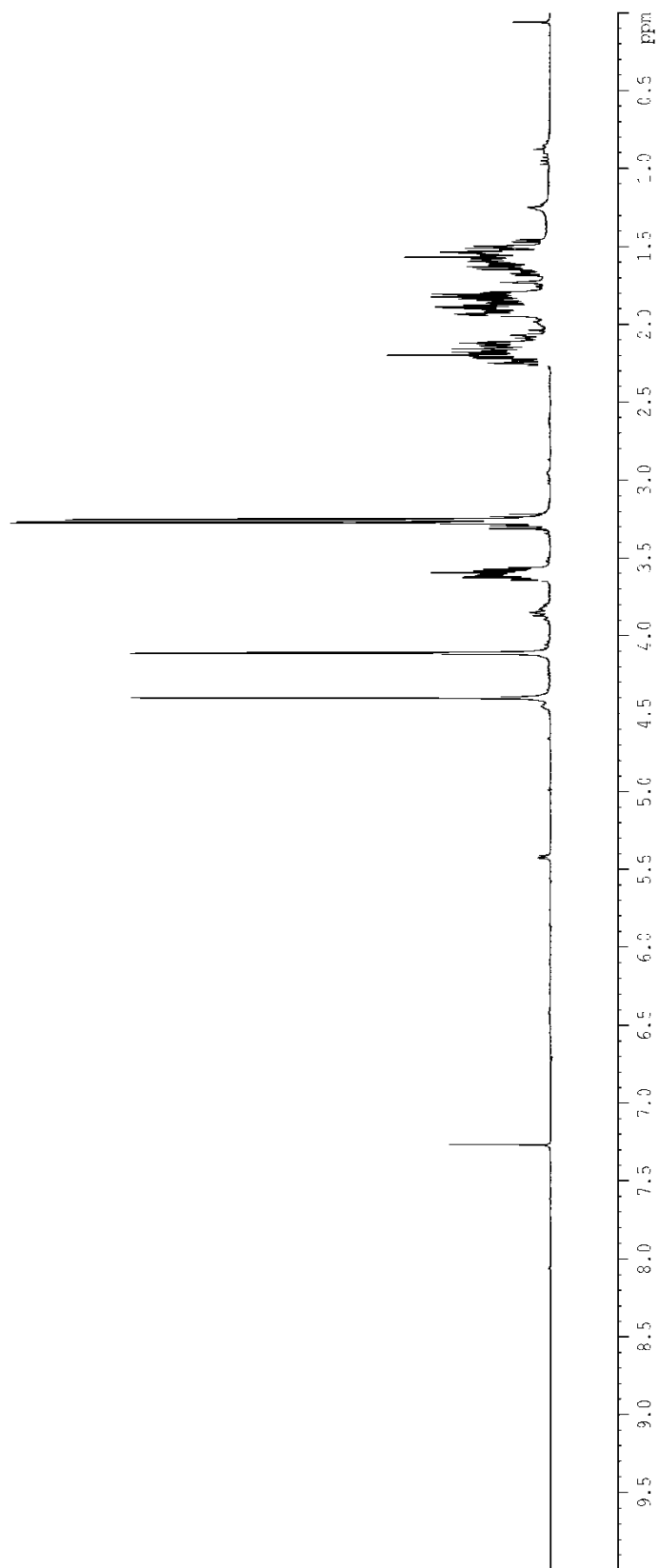
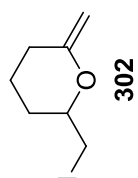


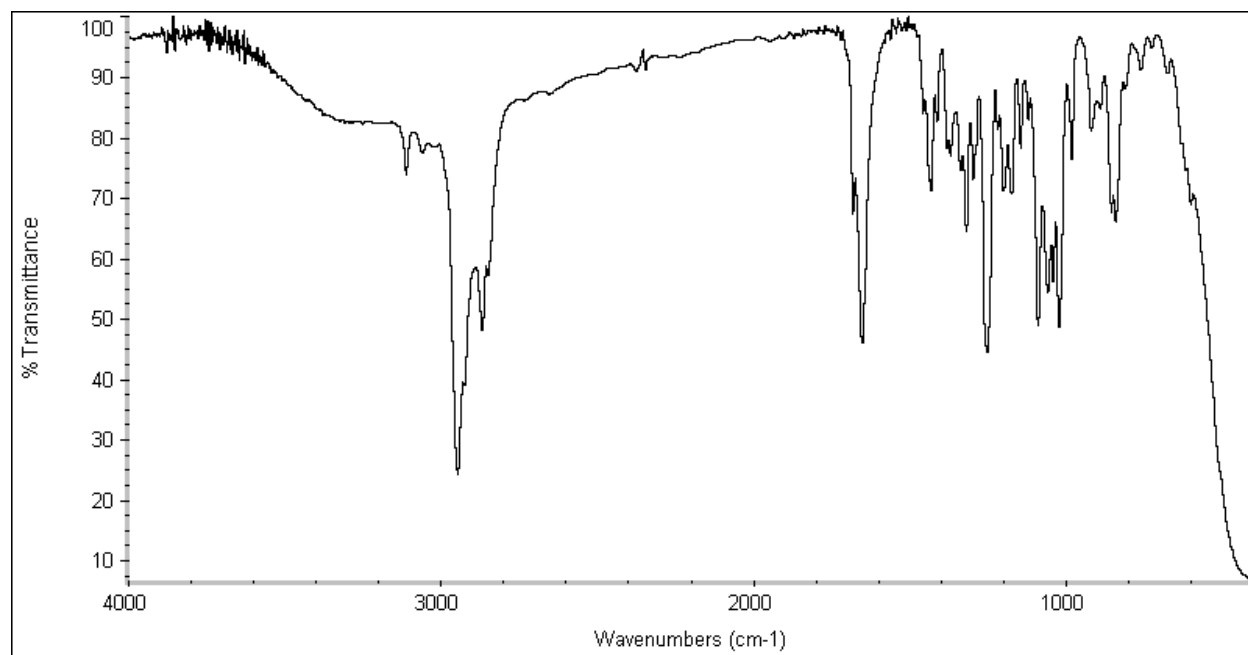
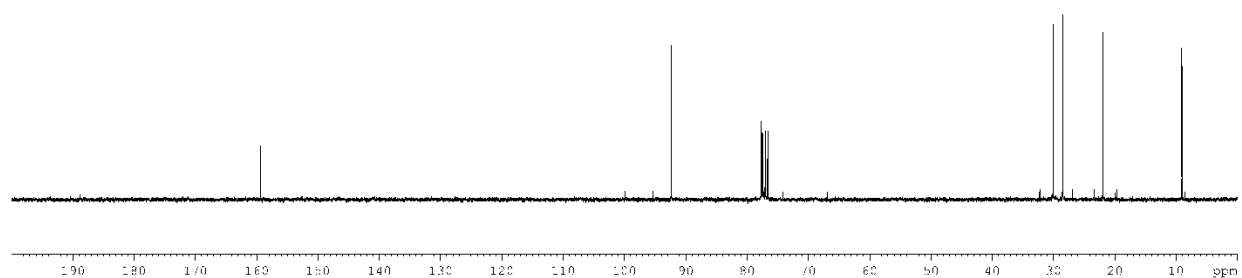
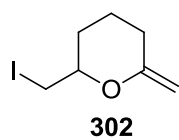


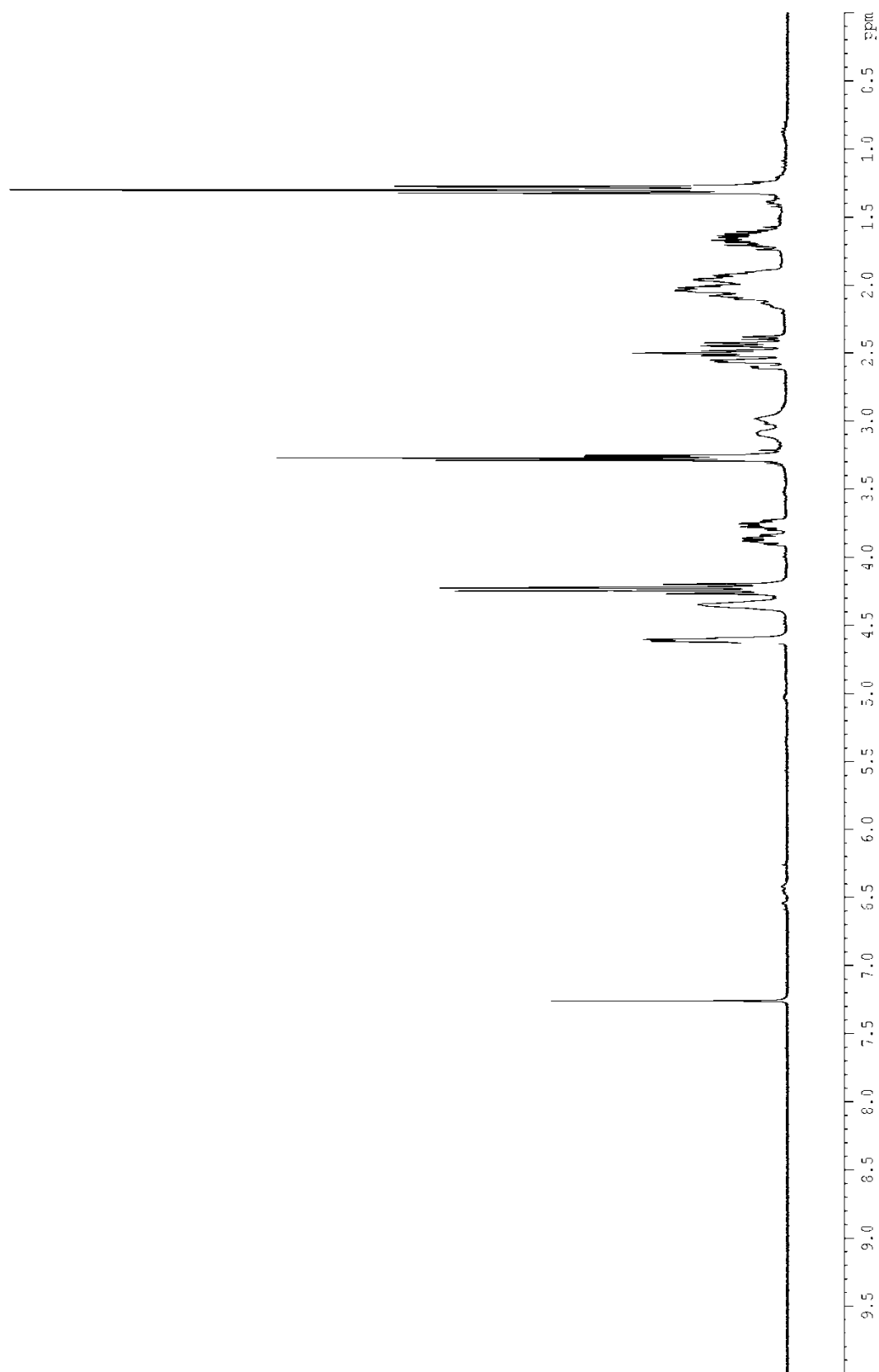
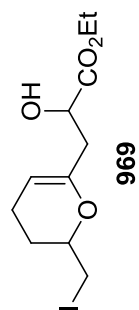
Appendix 3

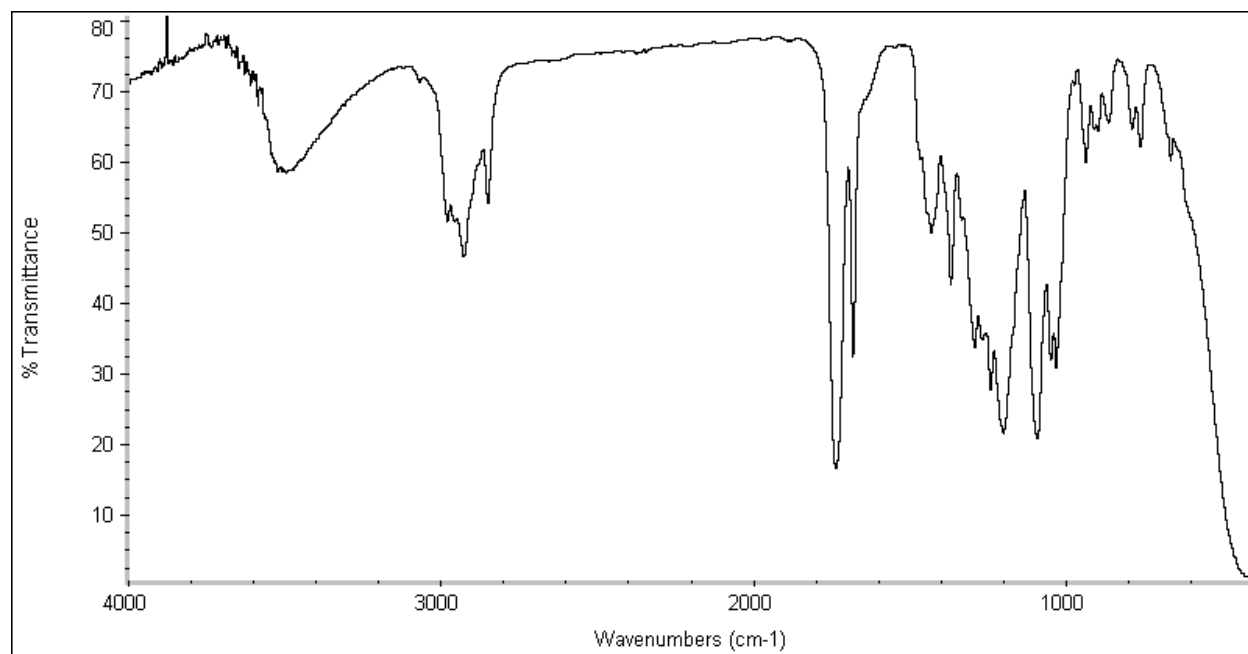
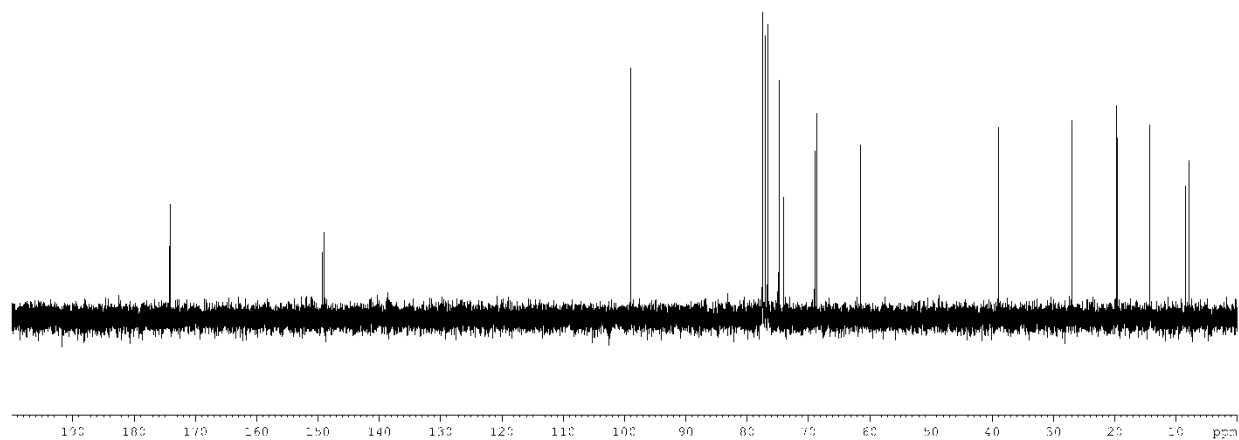
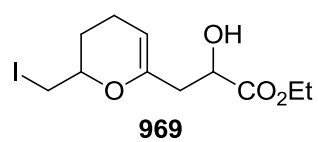
Selected Spectral Data for Chapter 4: Formation of Pyrans via Bi-Directional Carbonyl-Ene Reactions

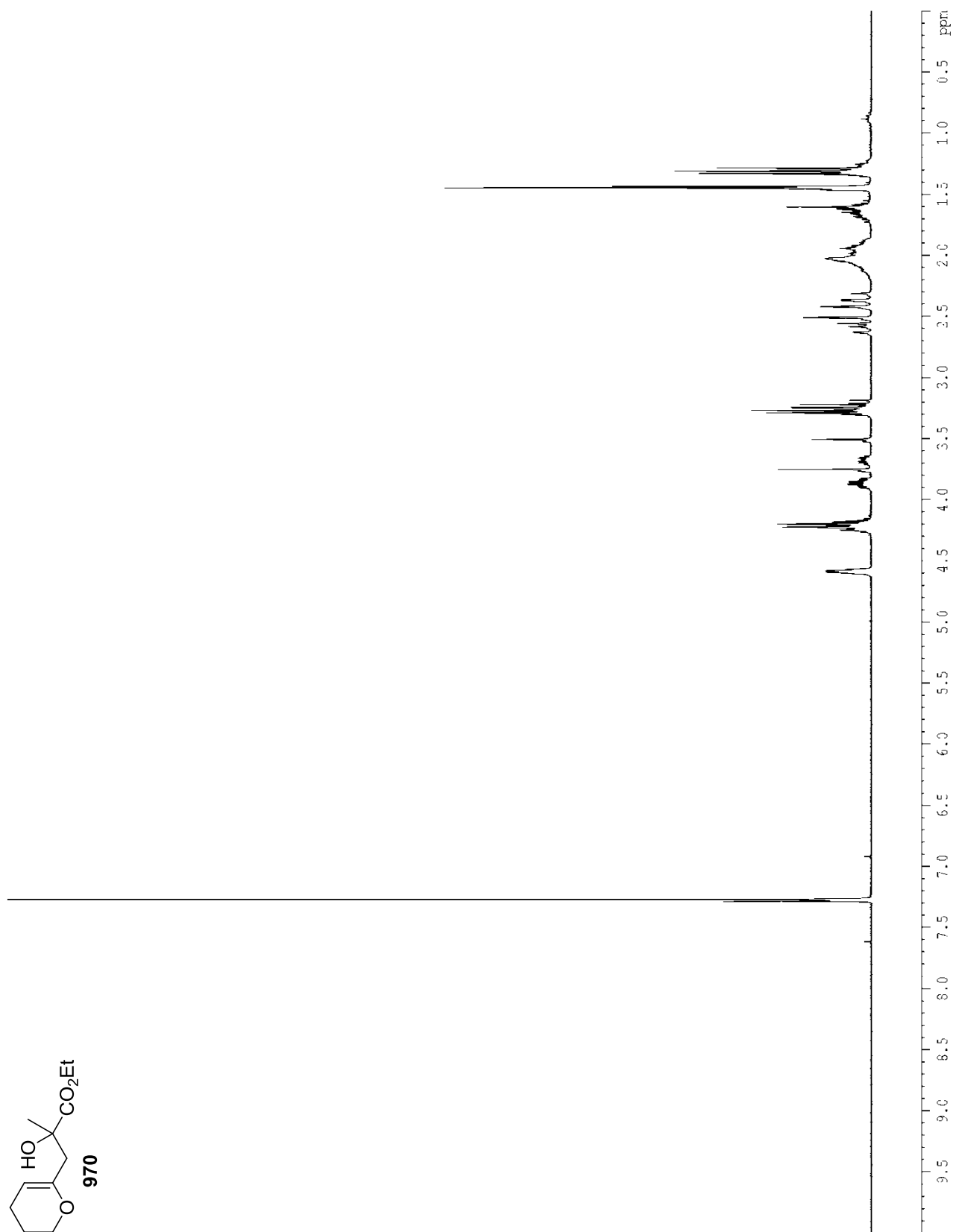
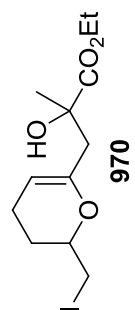


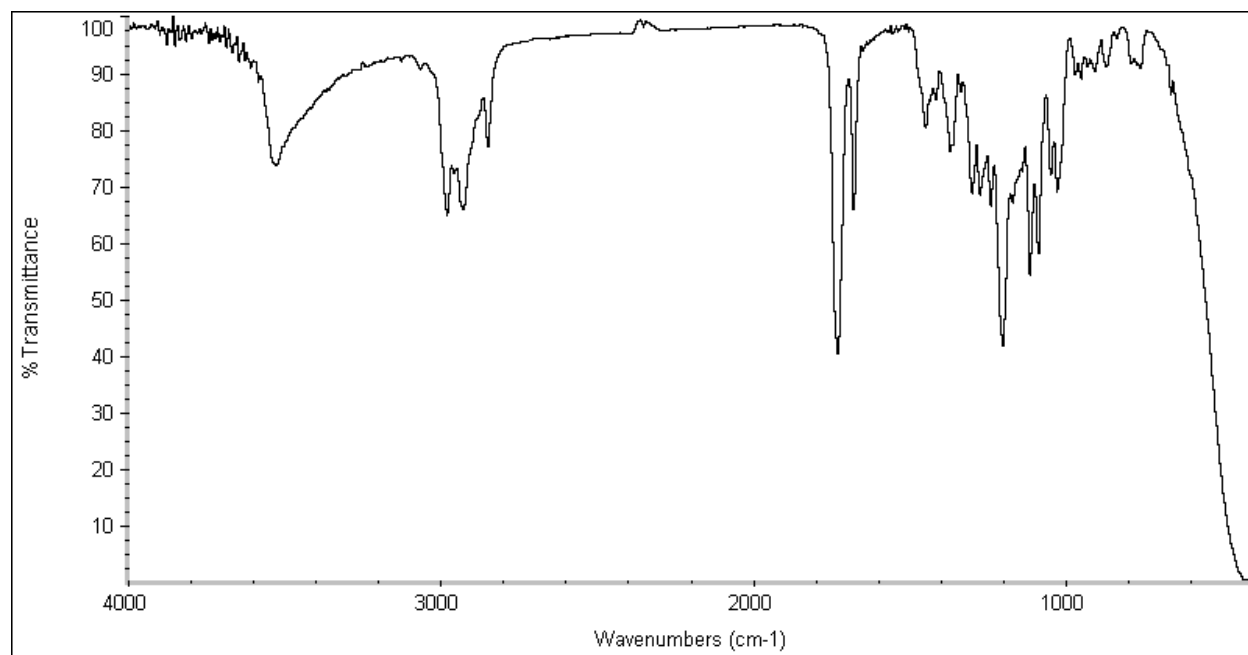
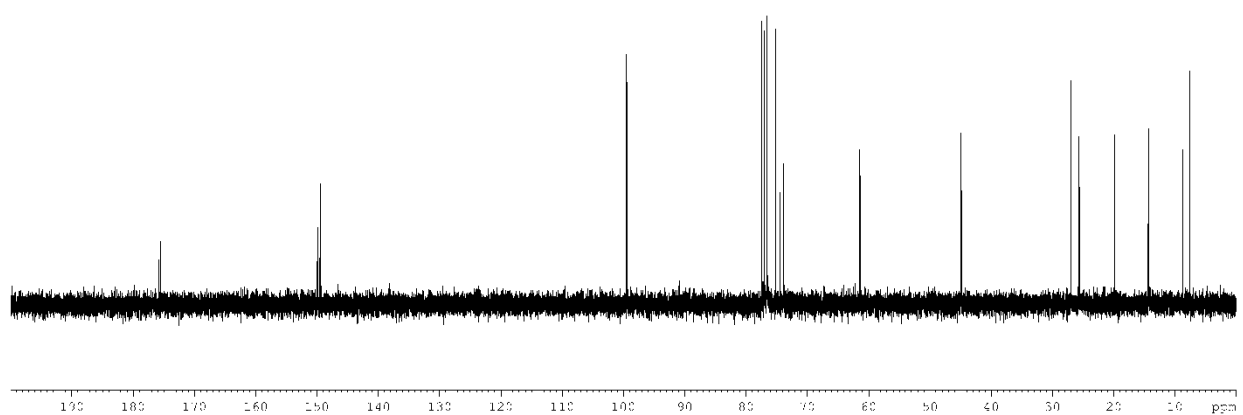
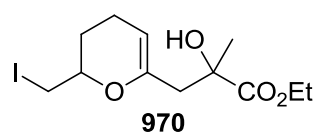


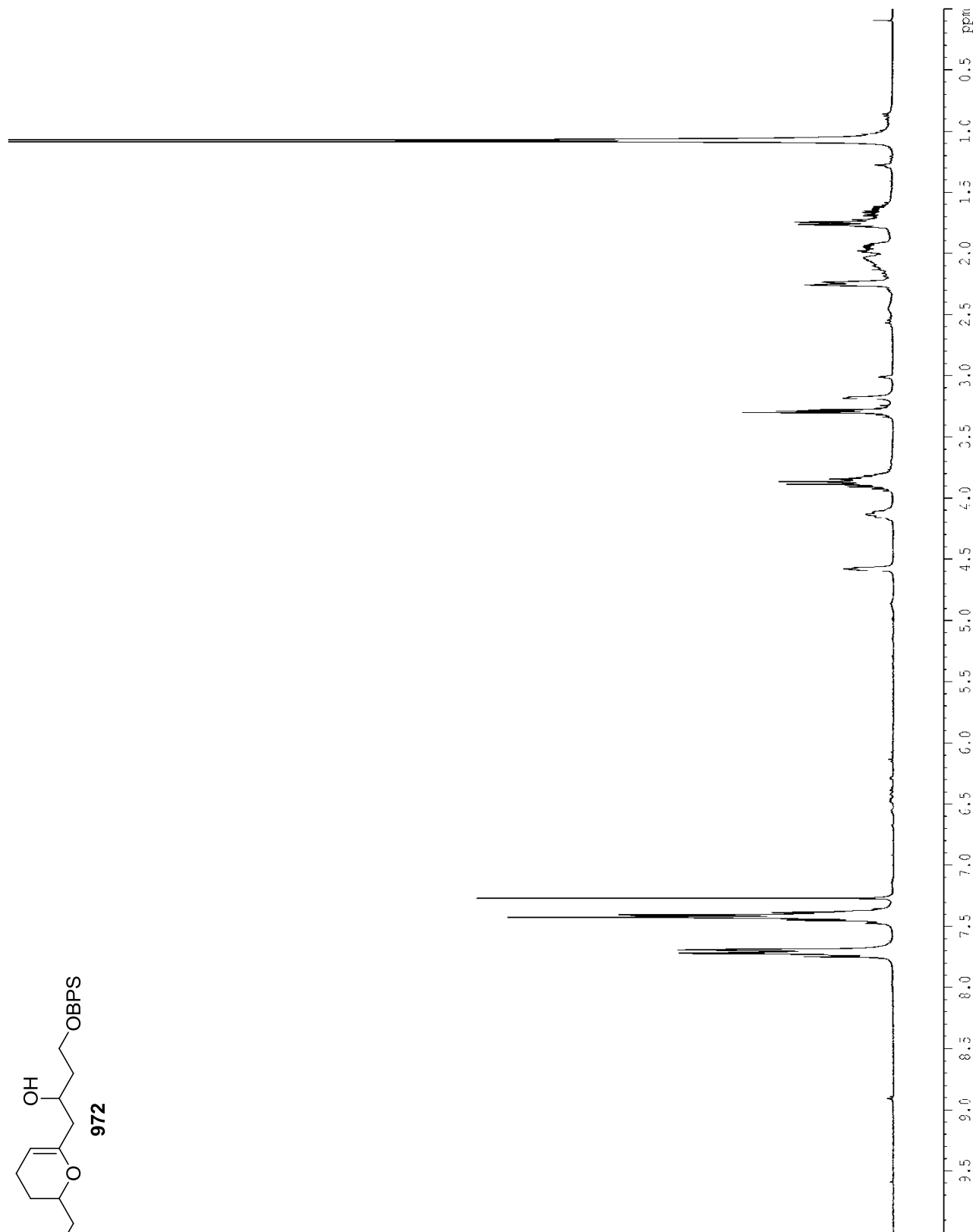
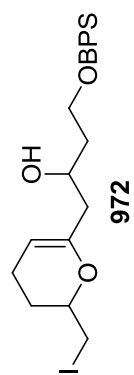


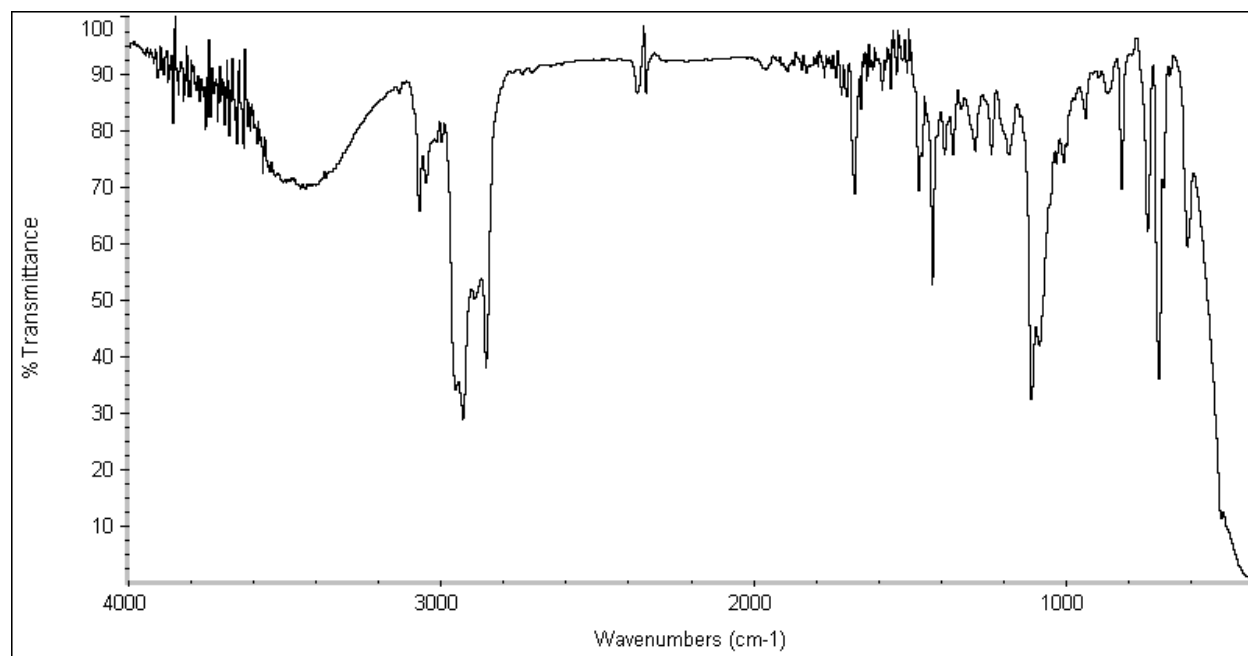
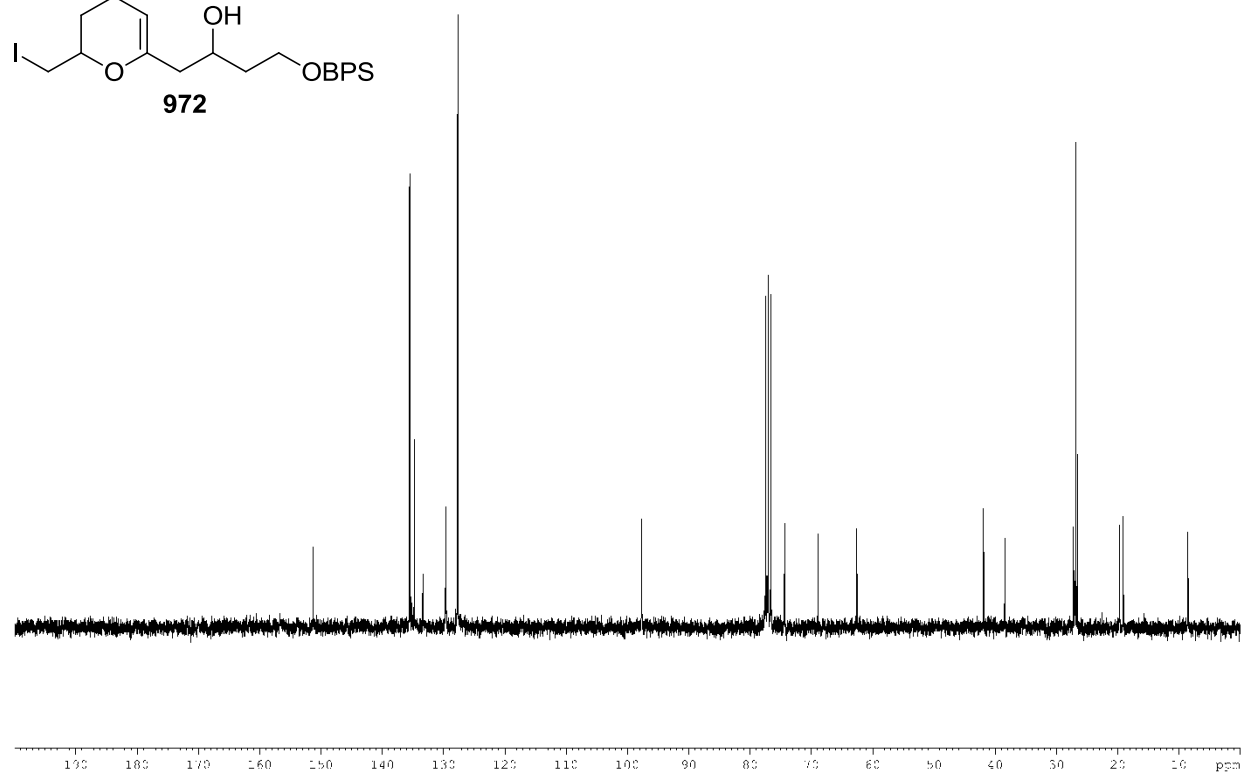
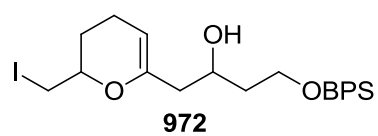


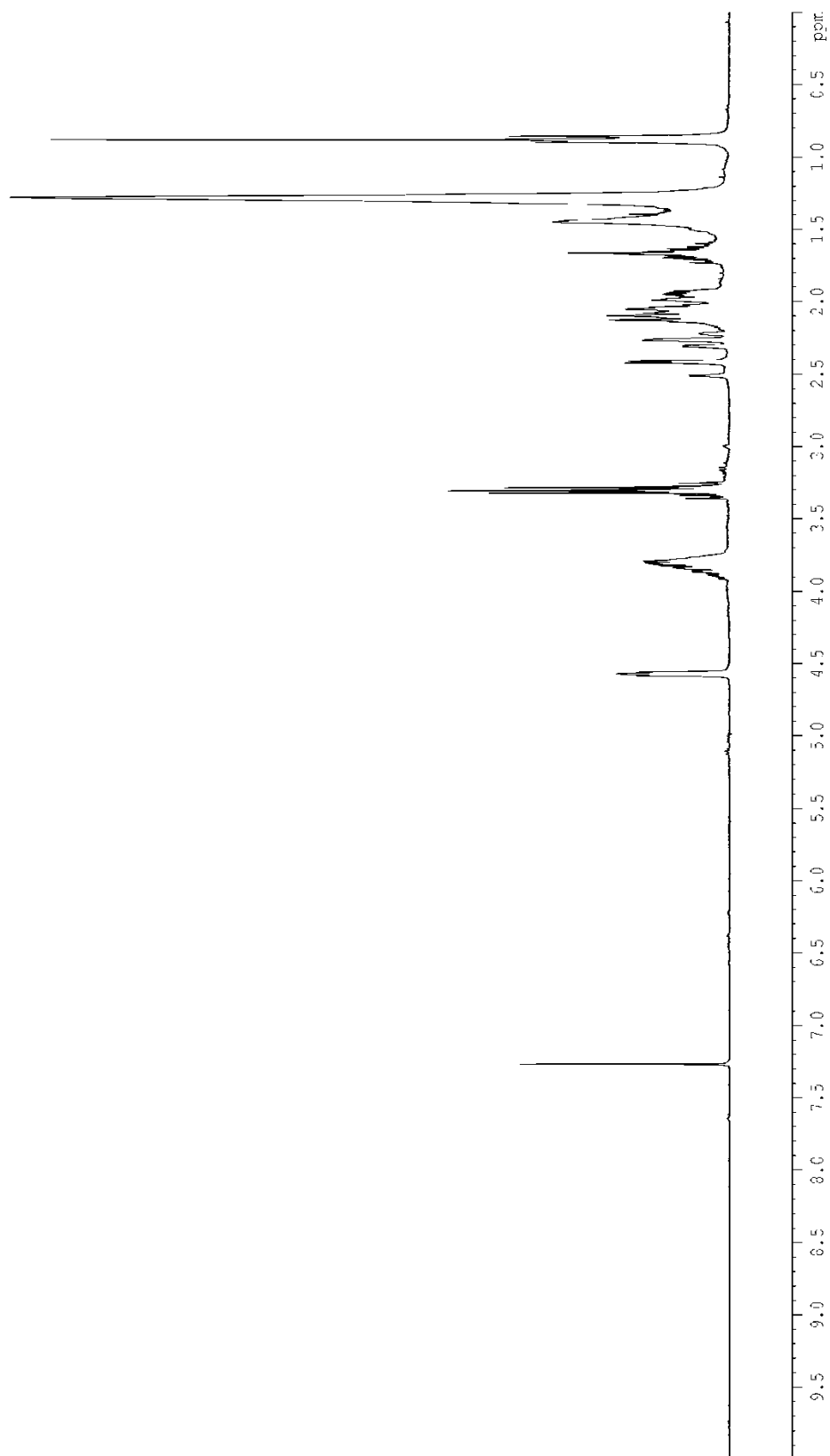
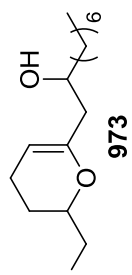


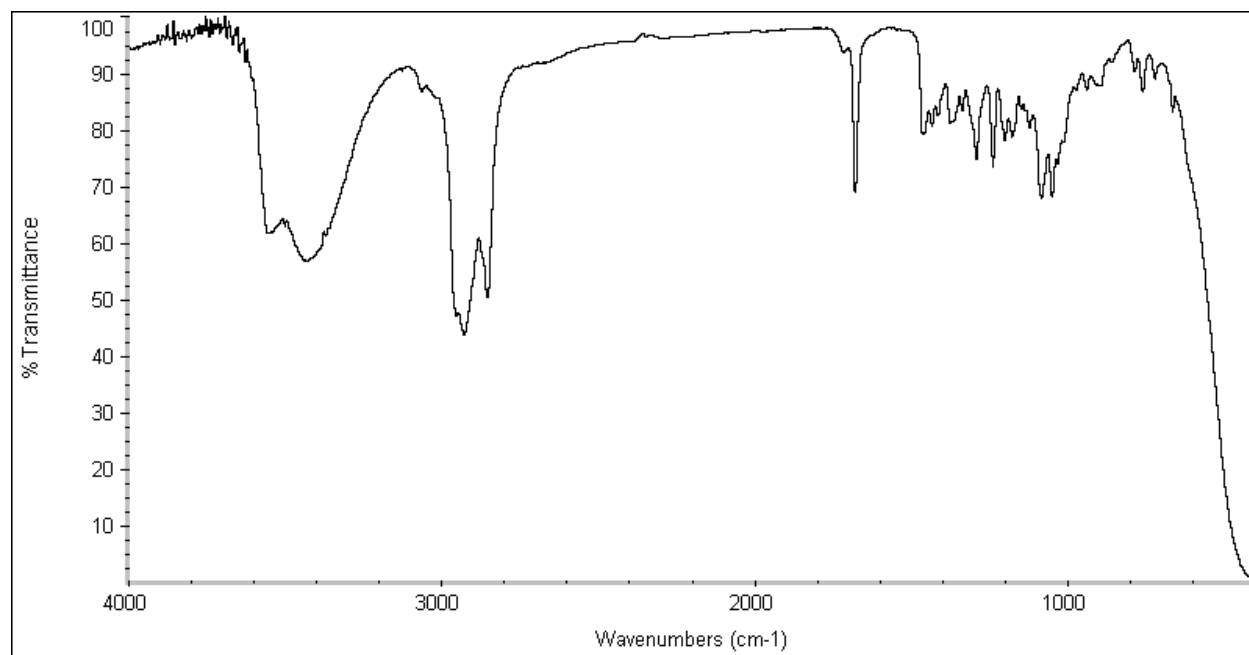
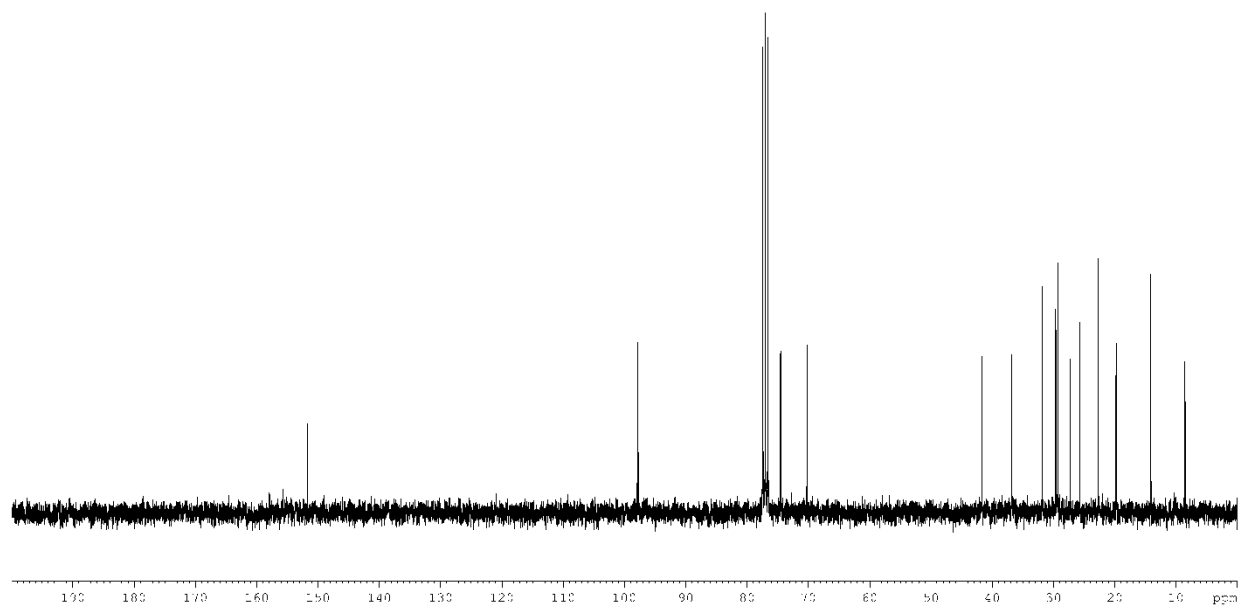
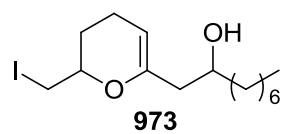


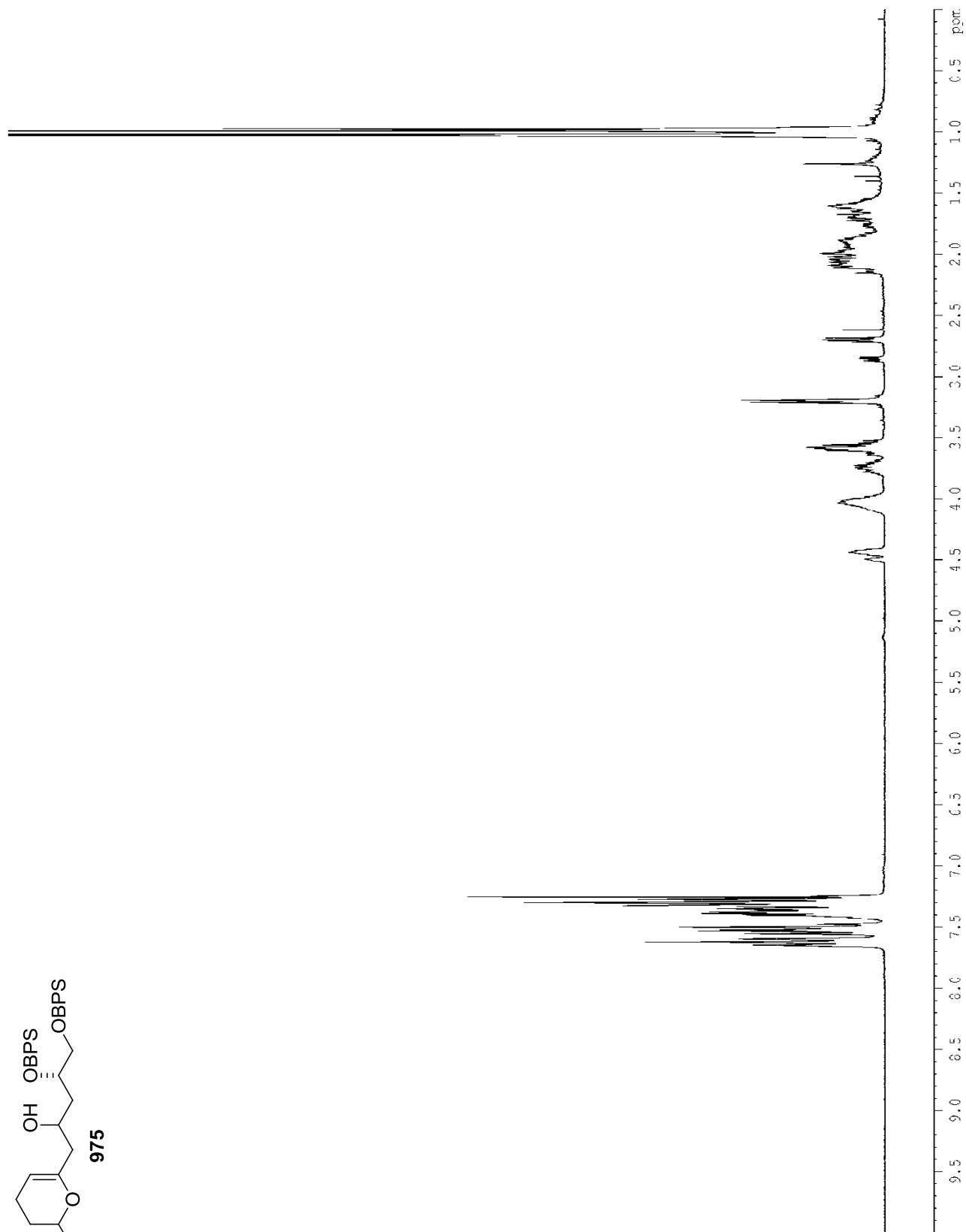
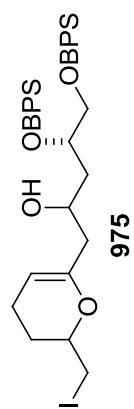


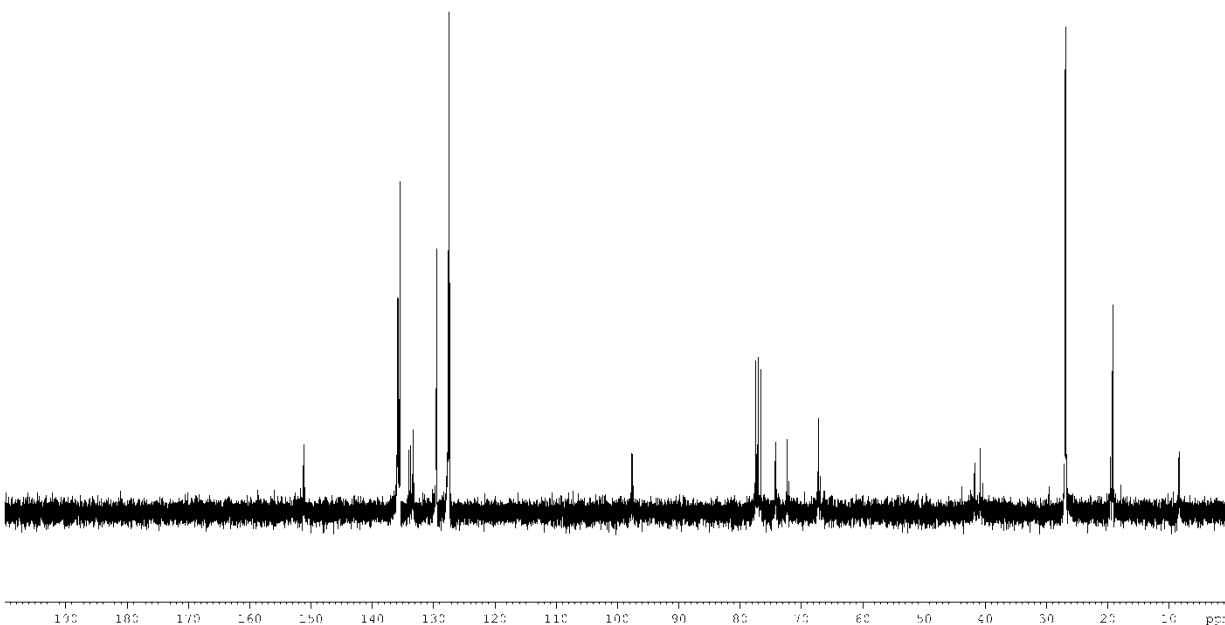


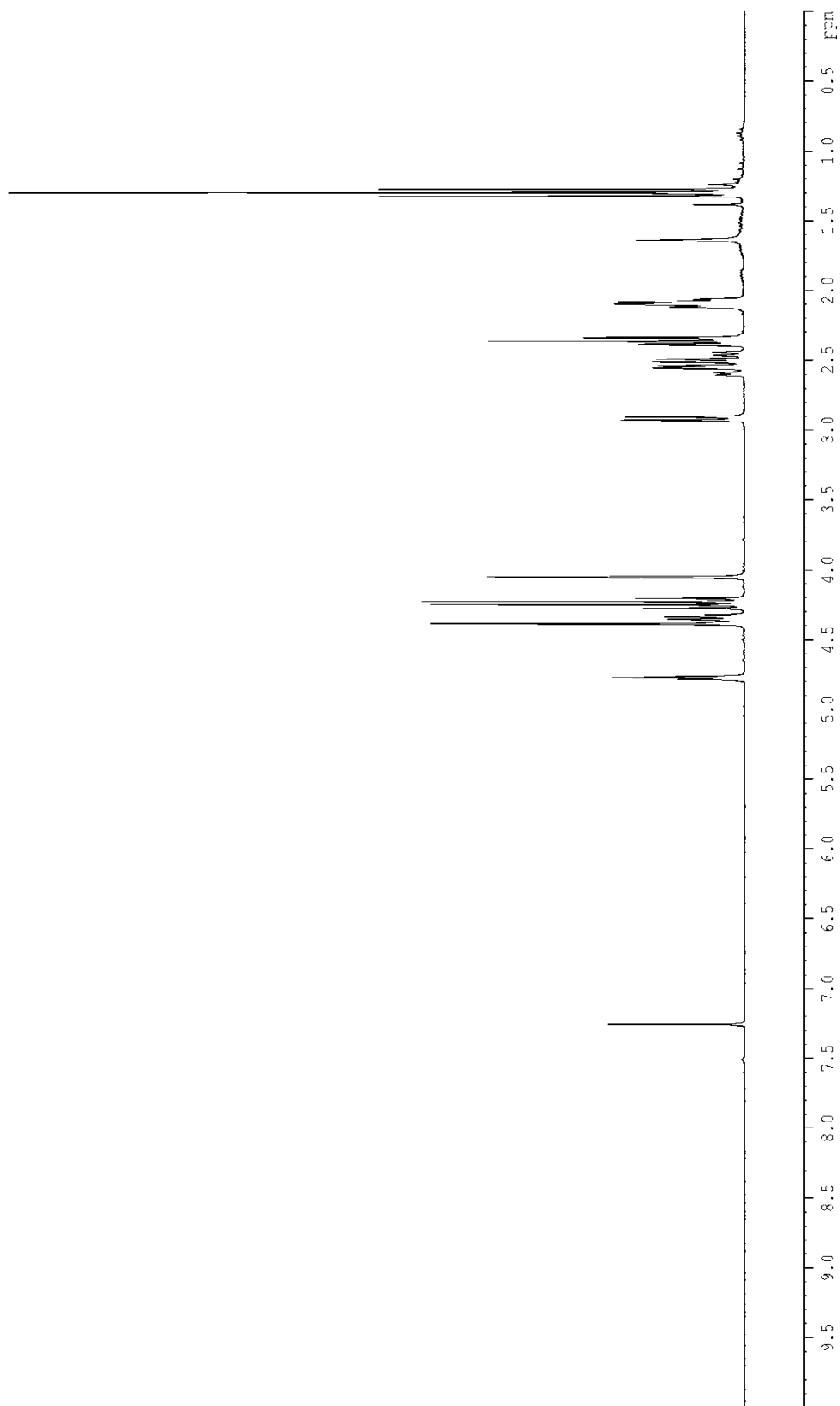
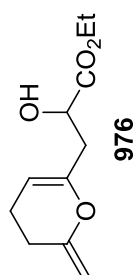


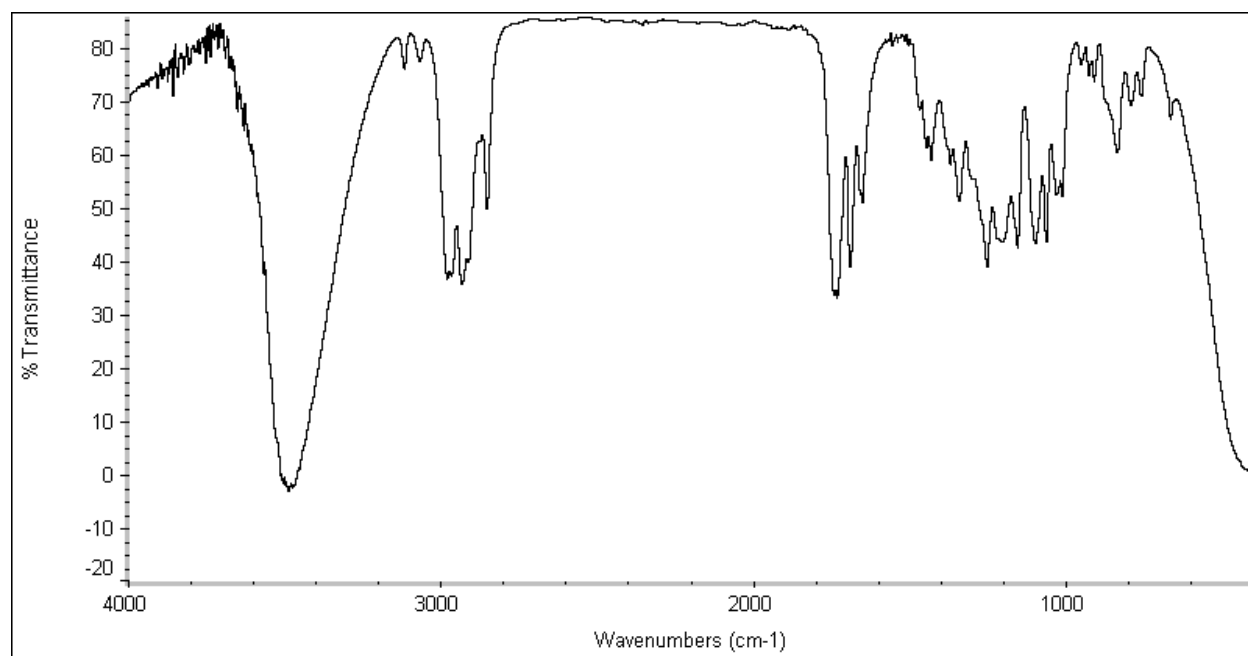
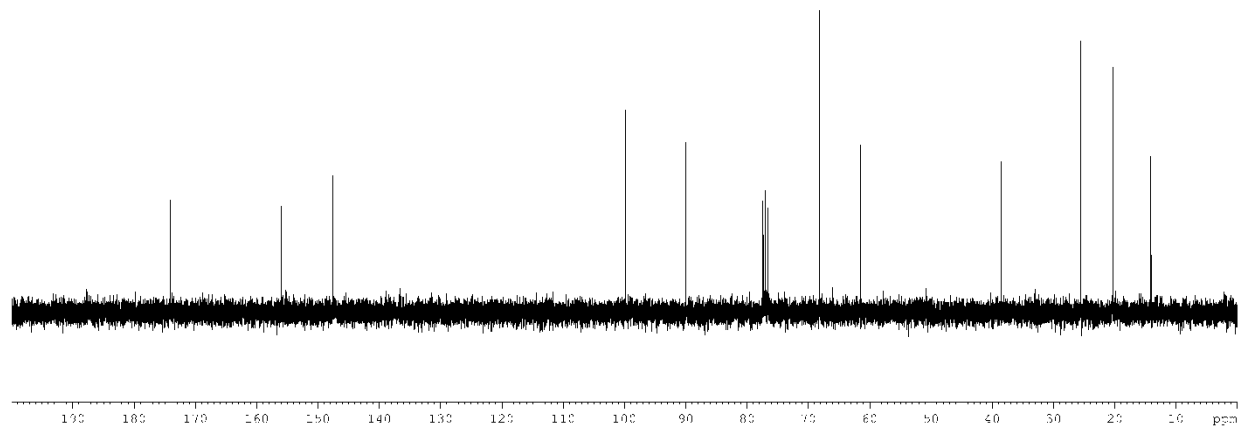
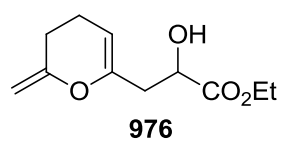


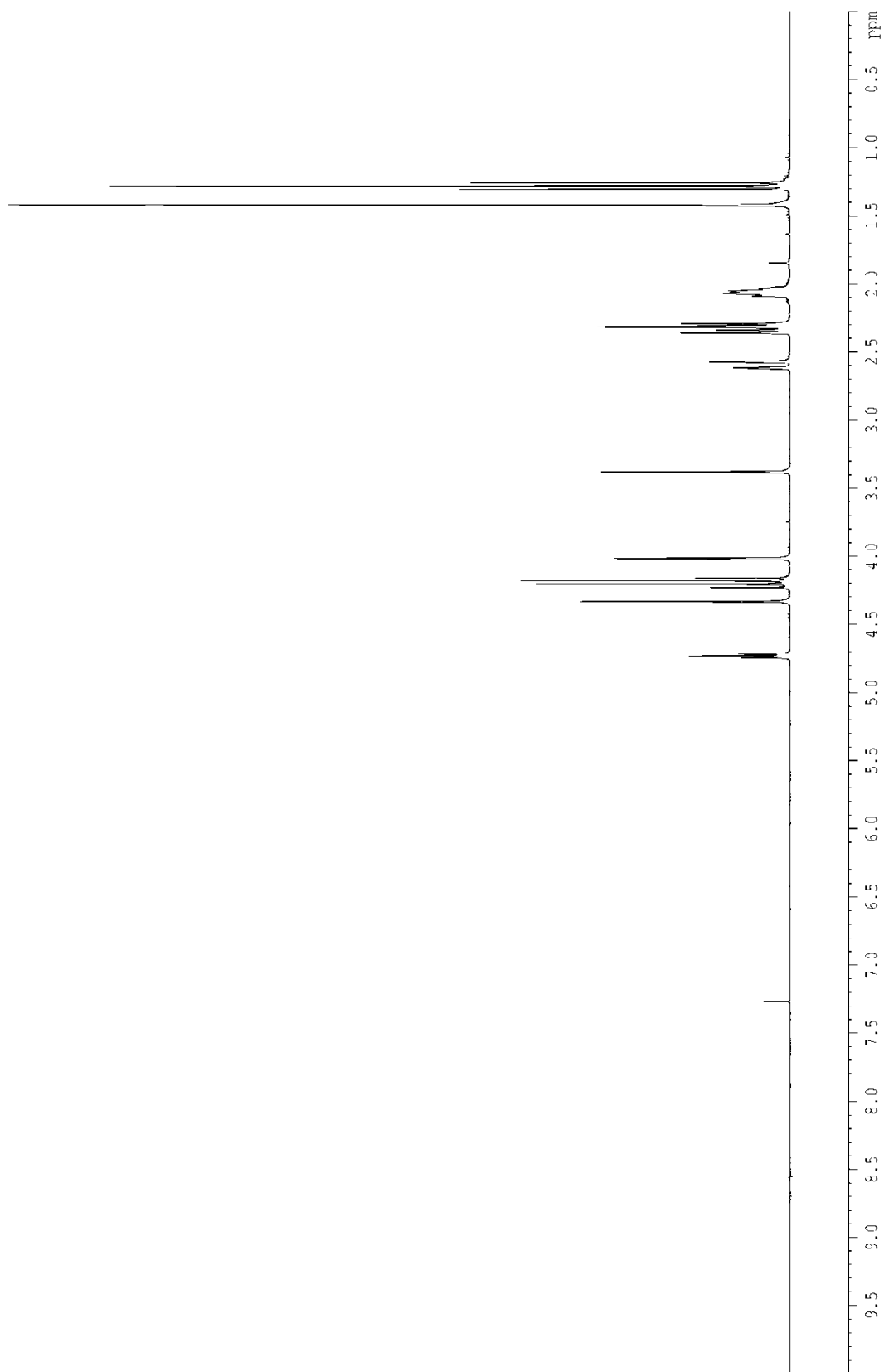
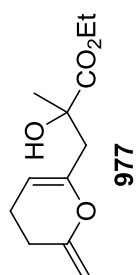


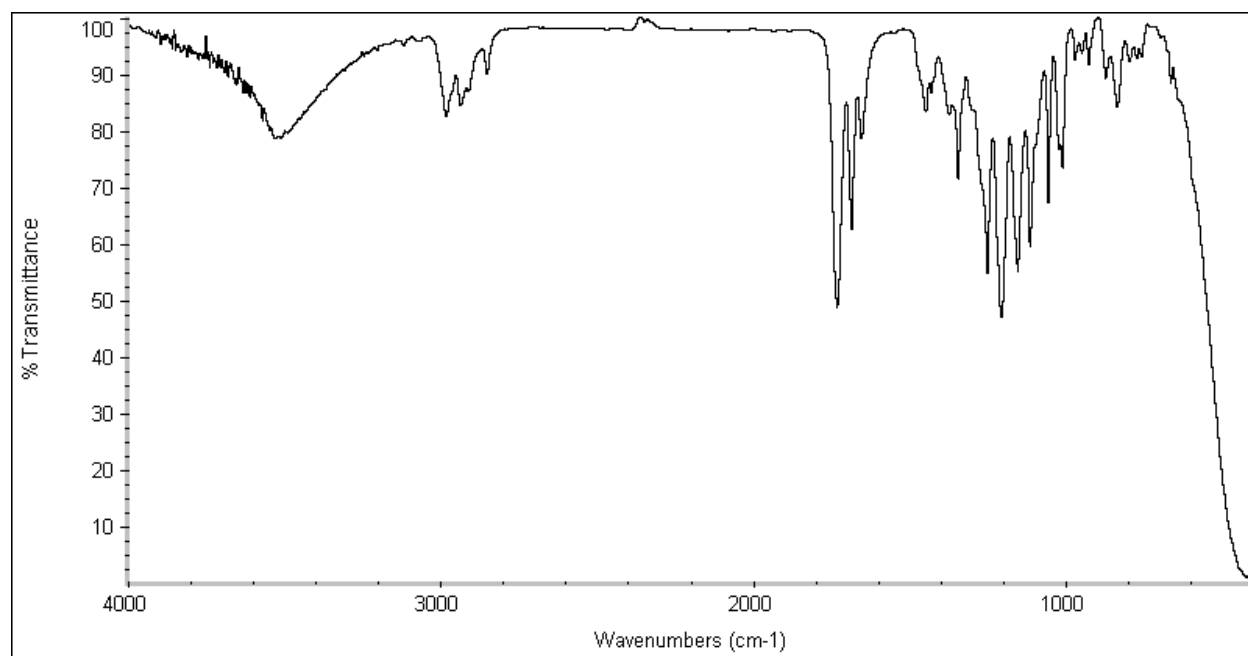
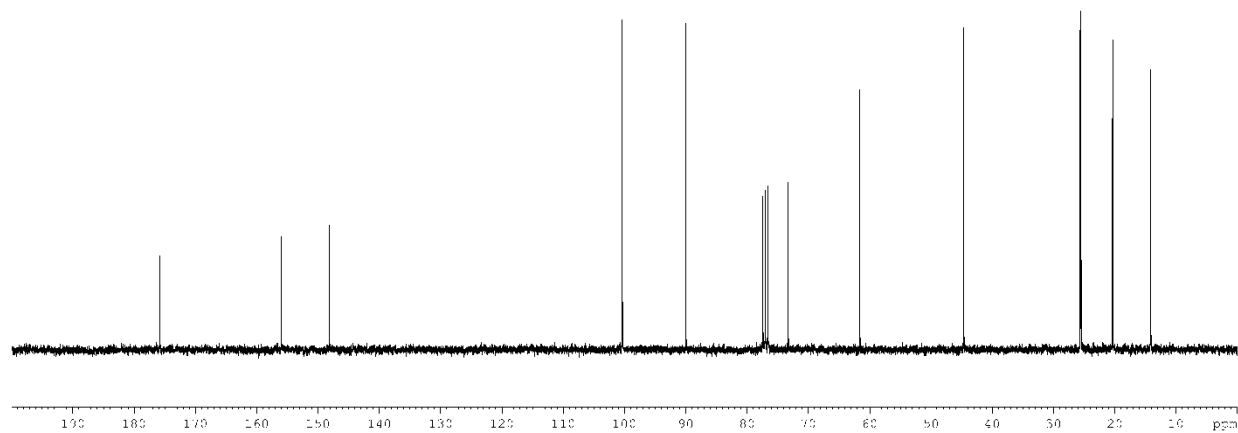
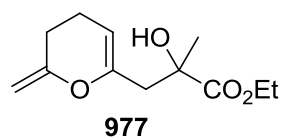


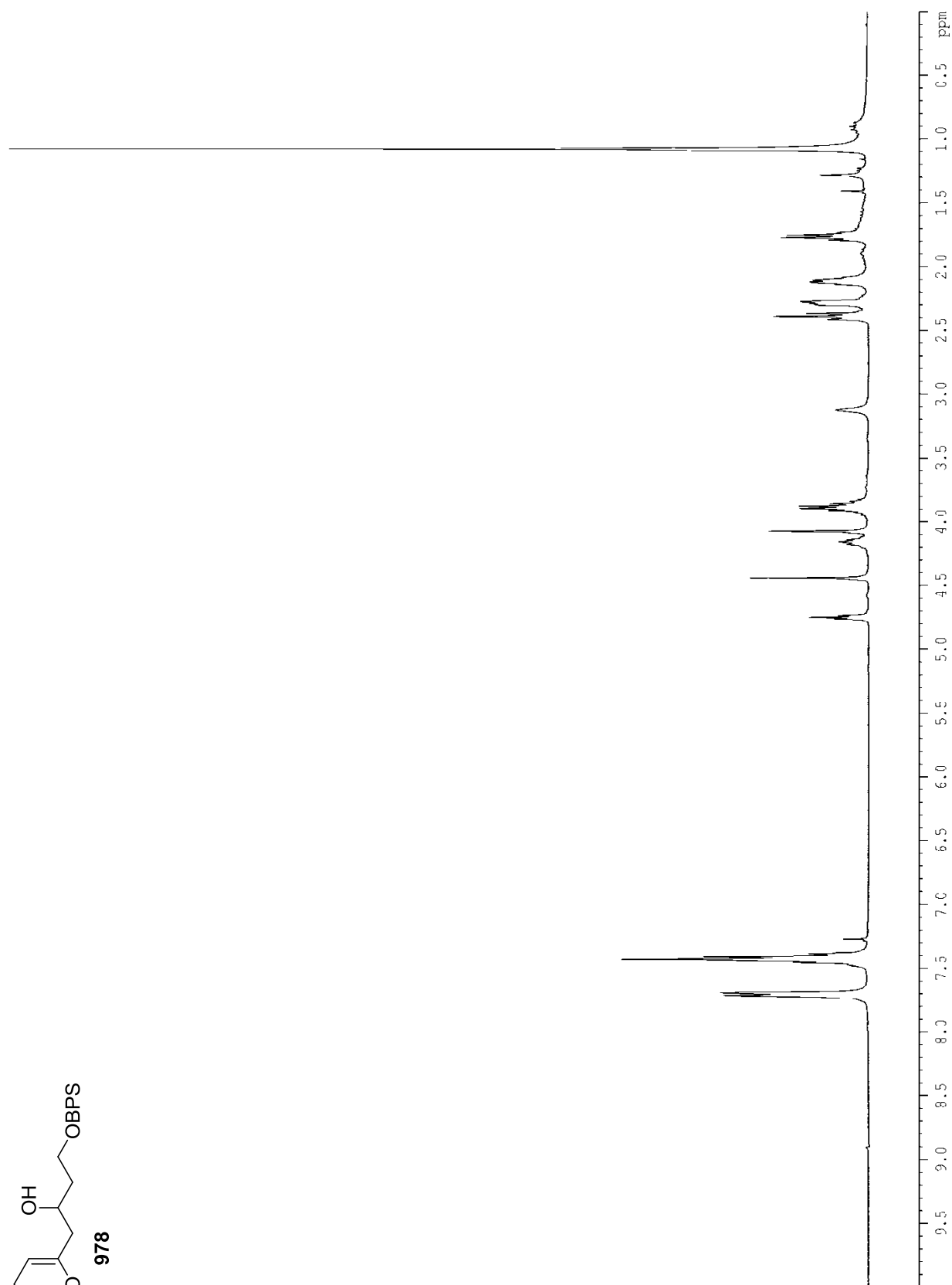
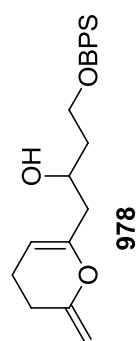


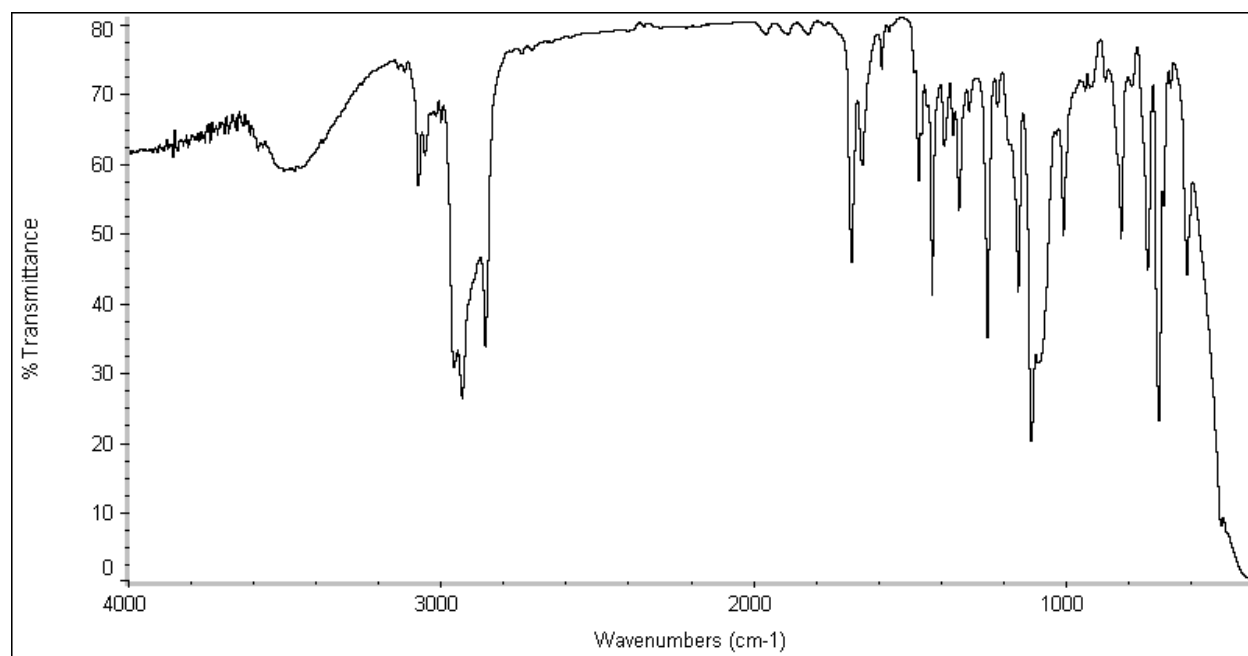
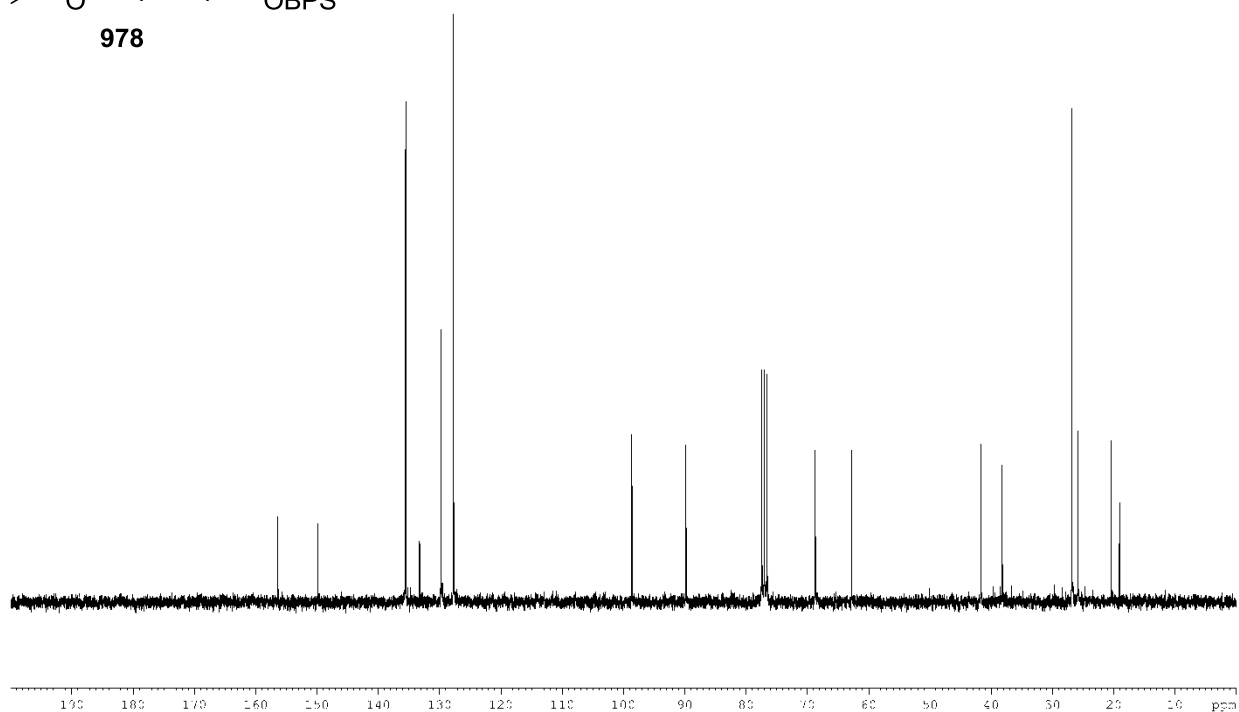
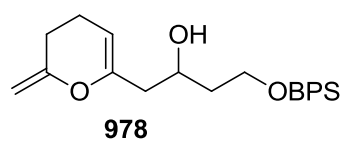




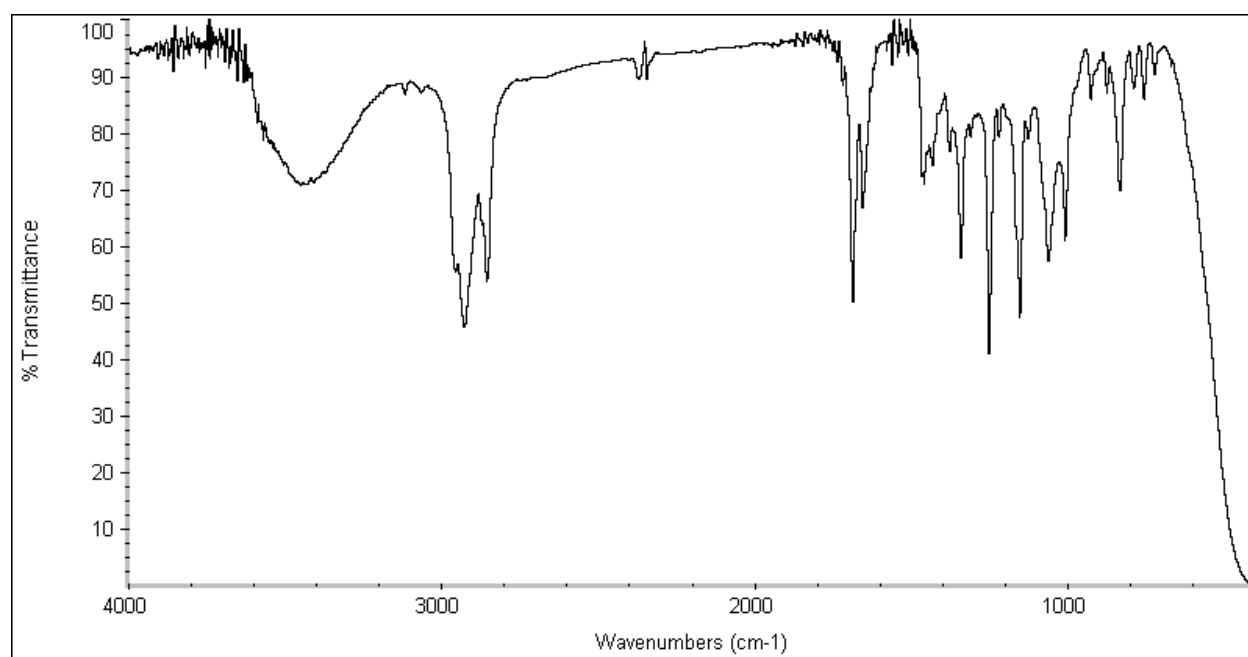
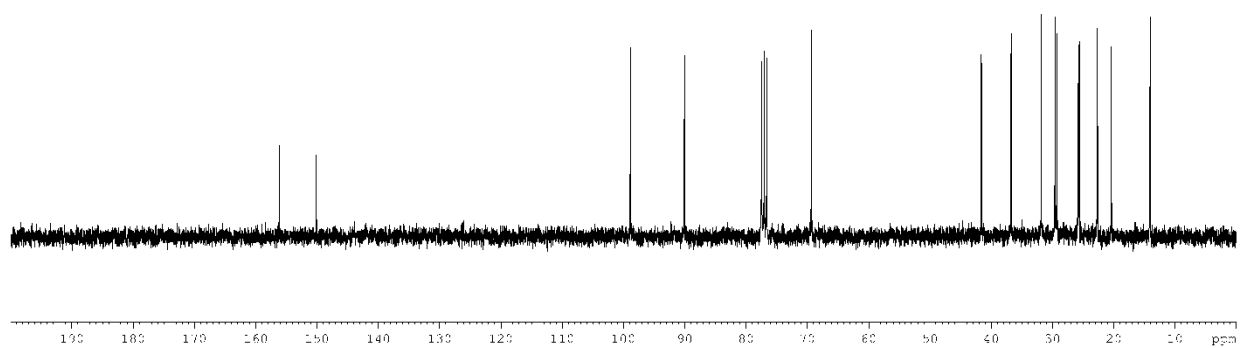


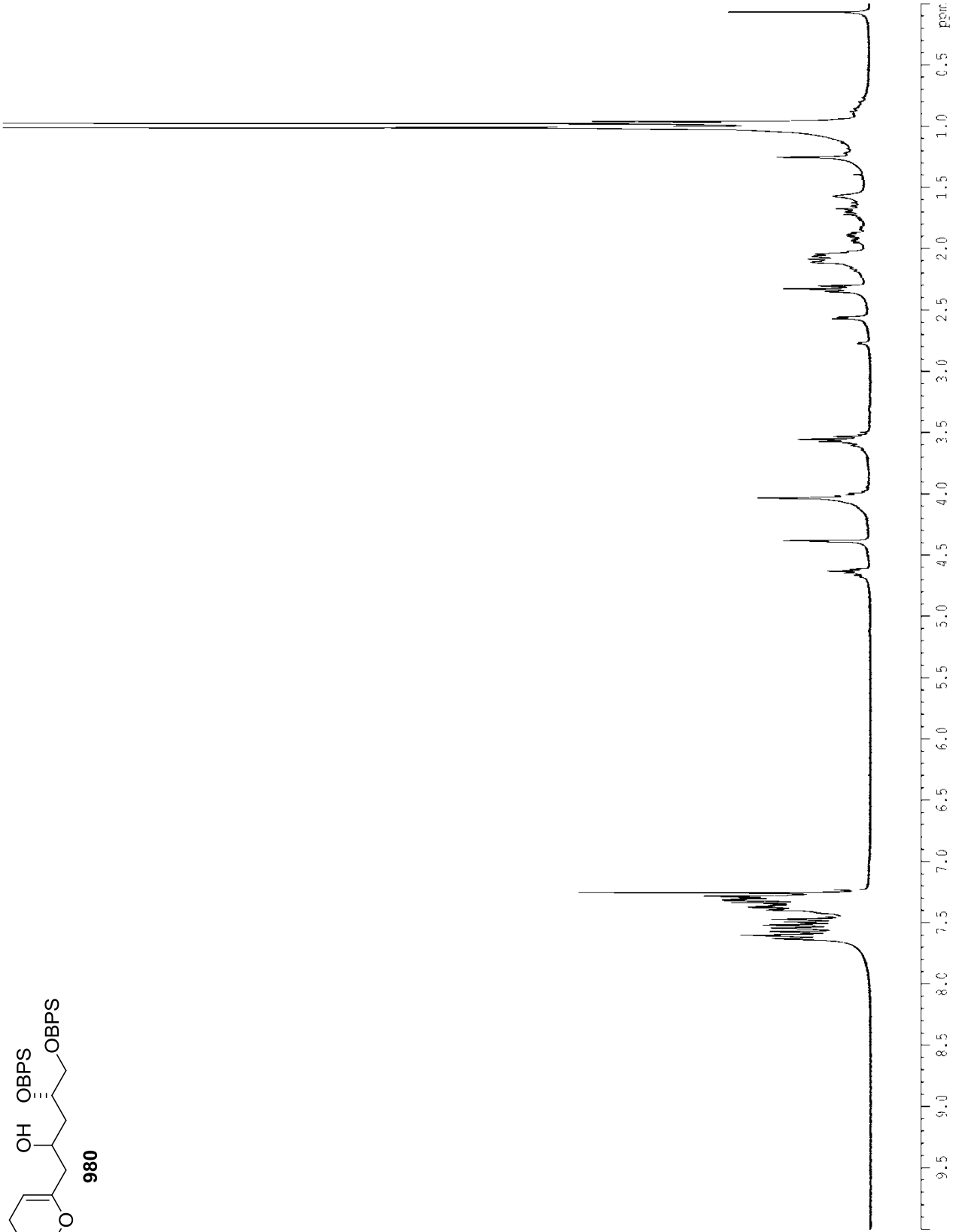


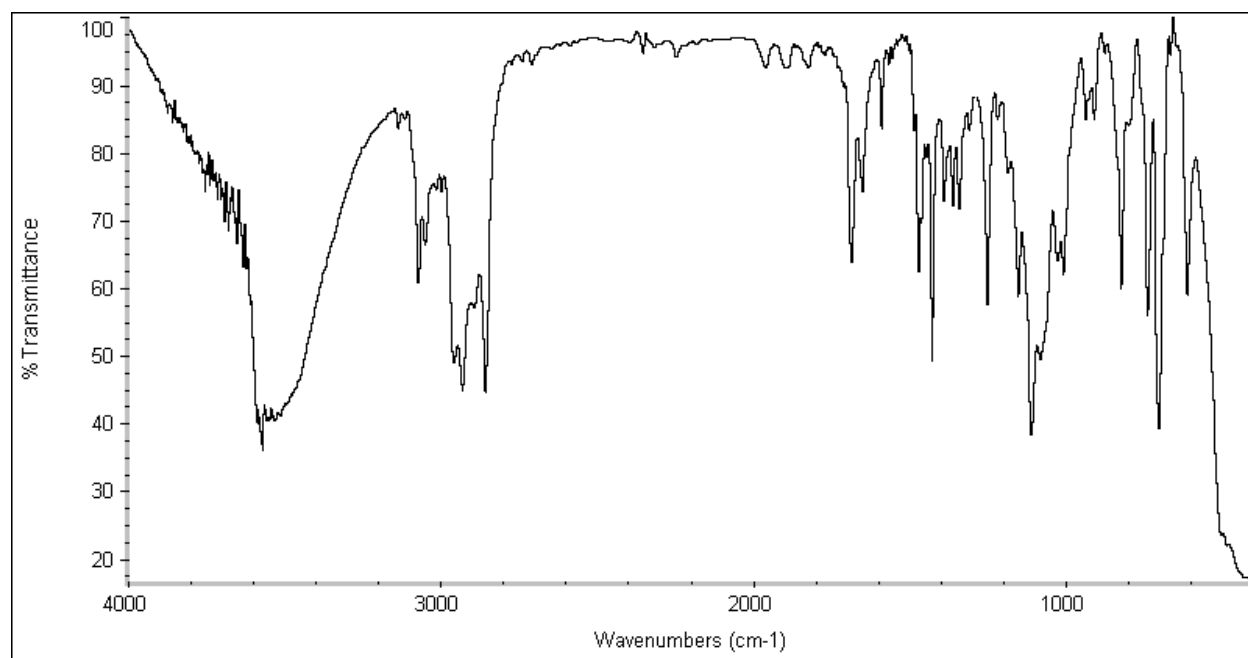
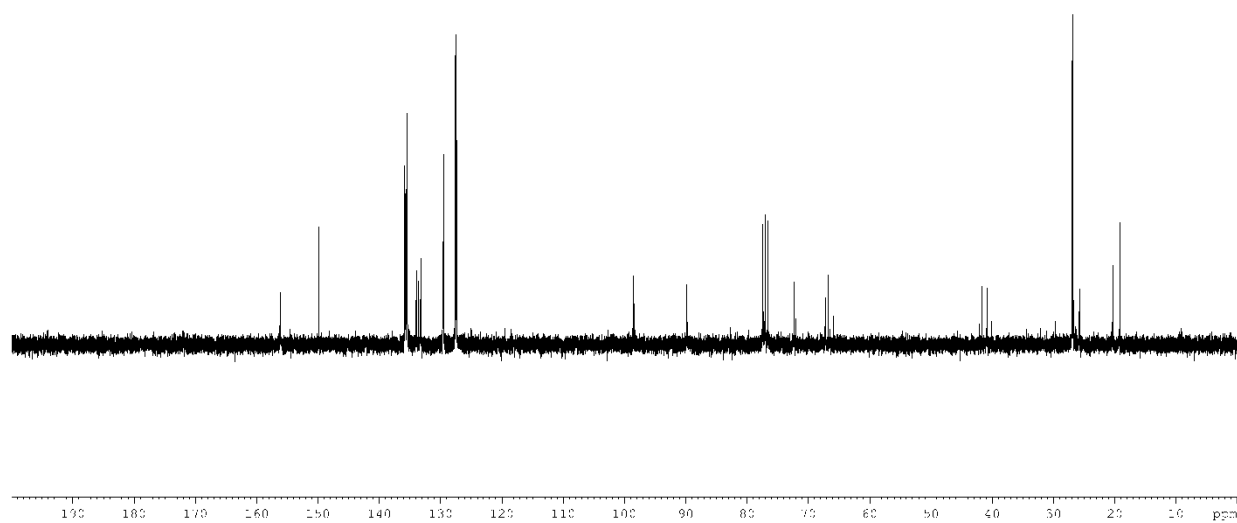
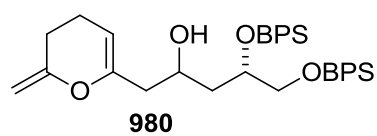


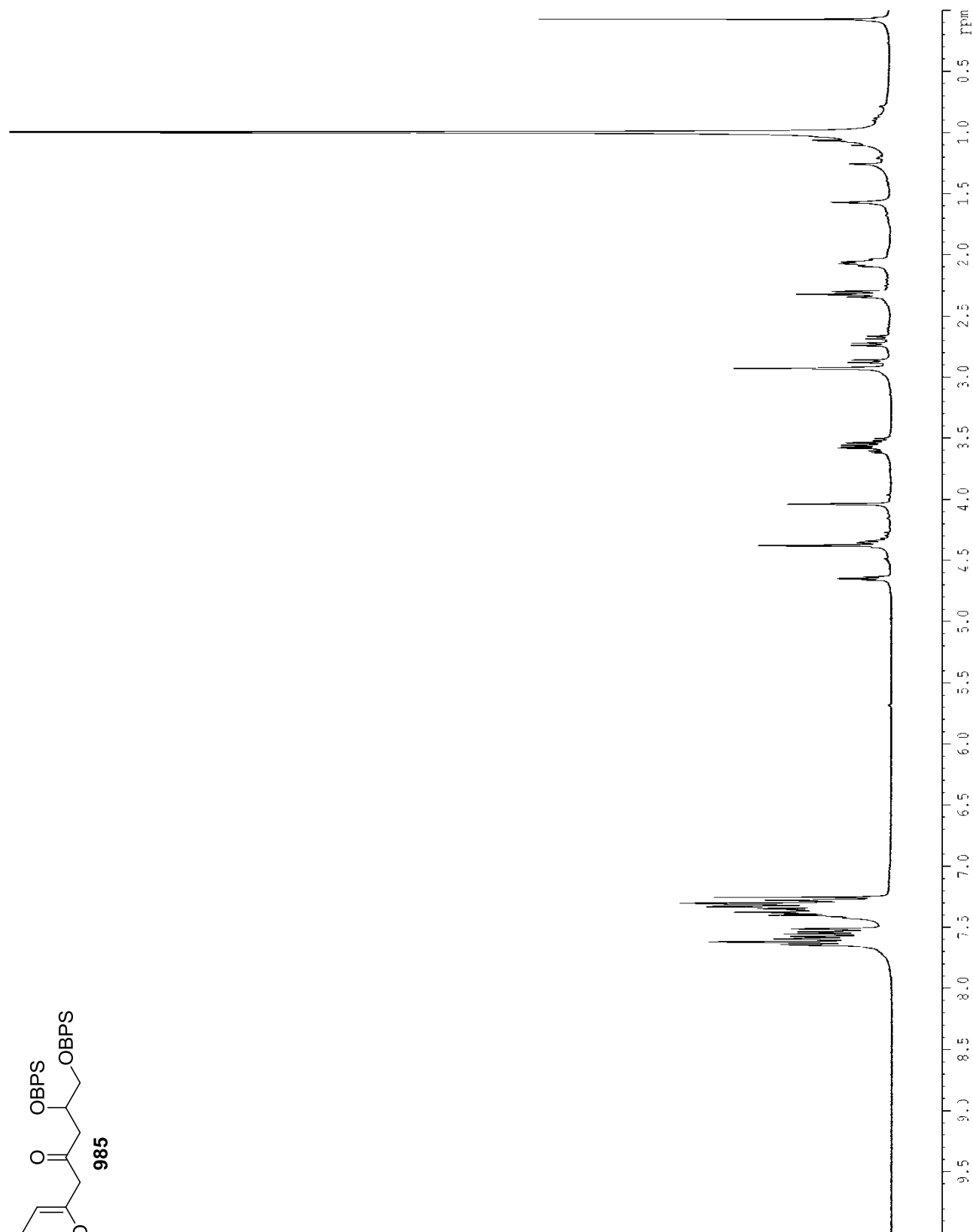
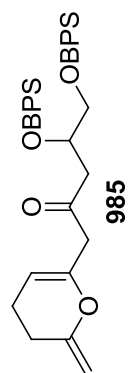


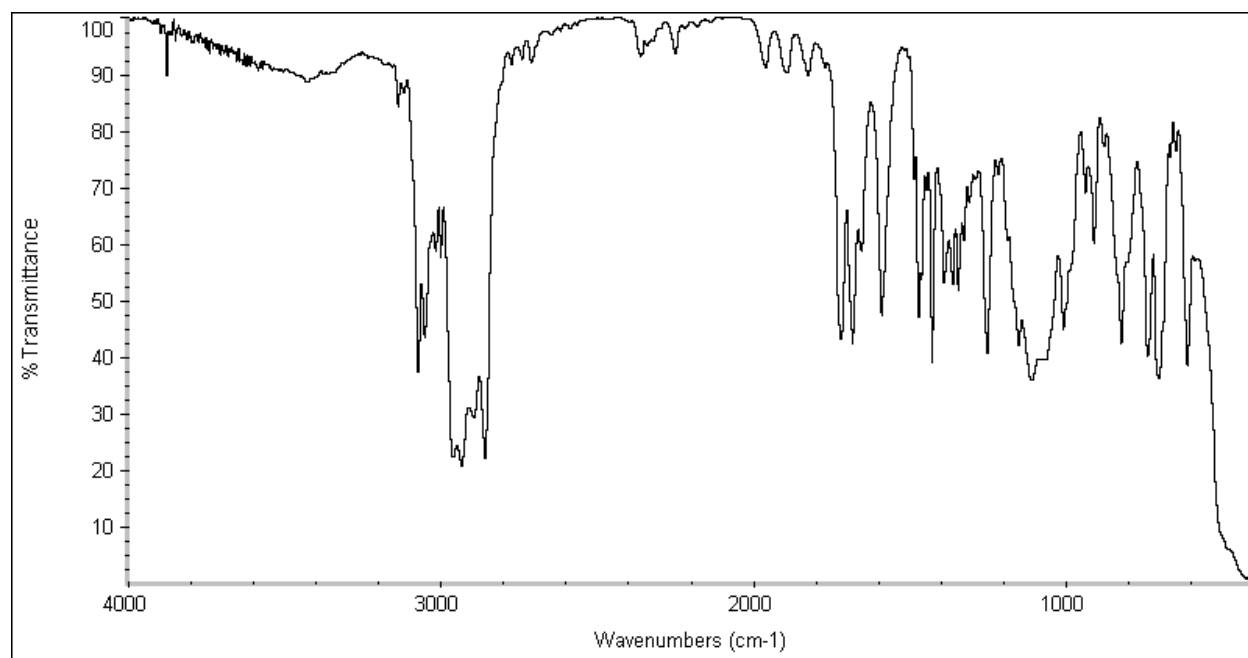
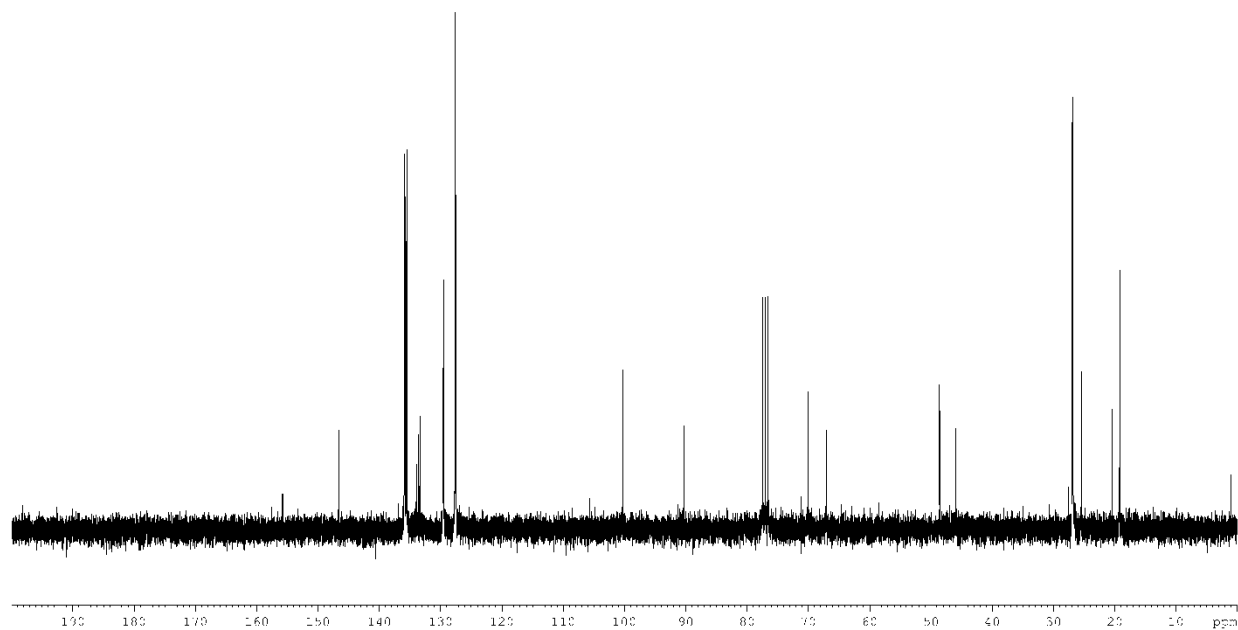
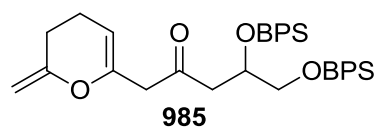


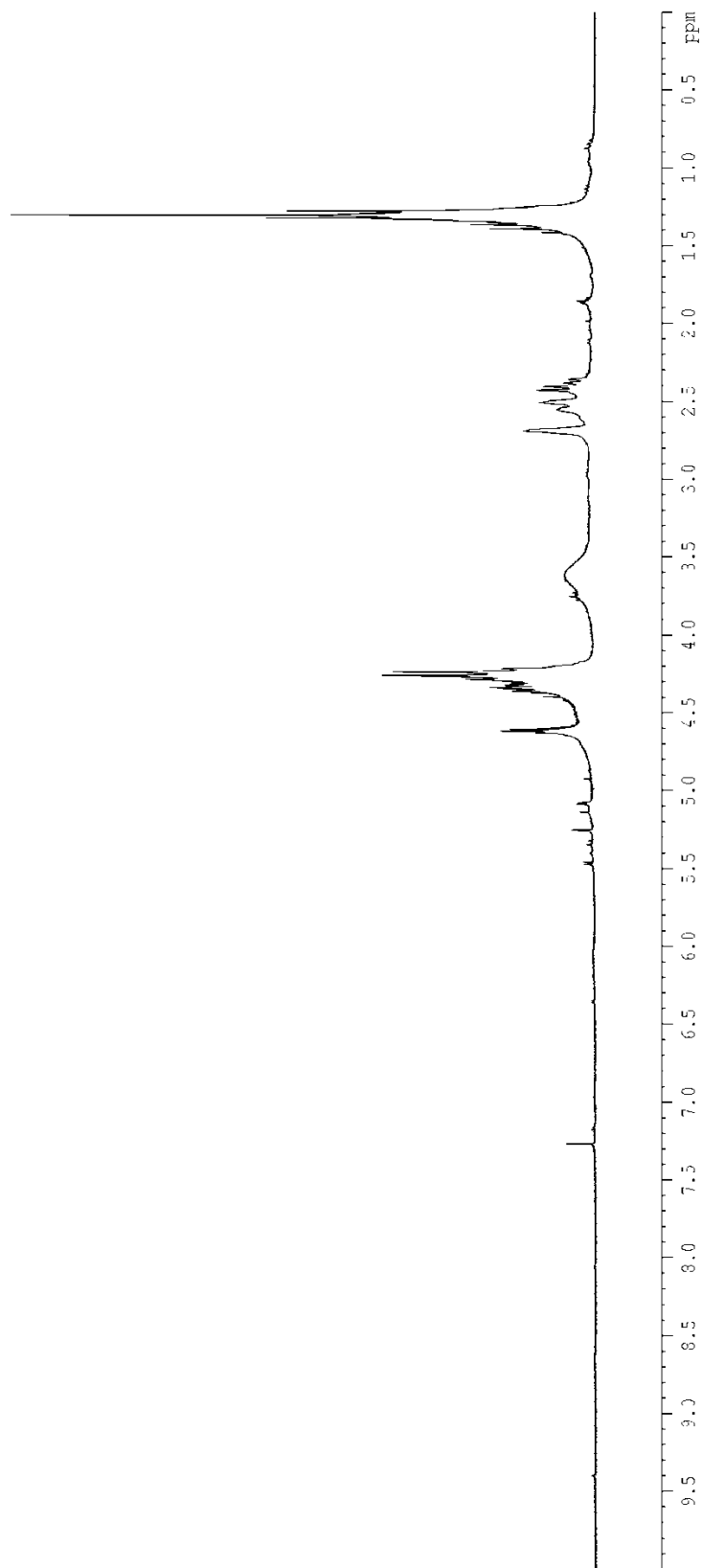
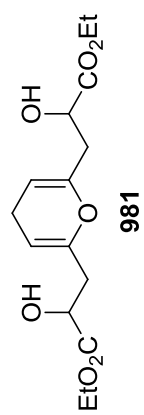


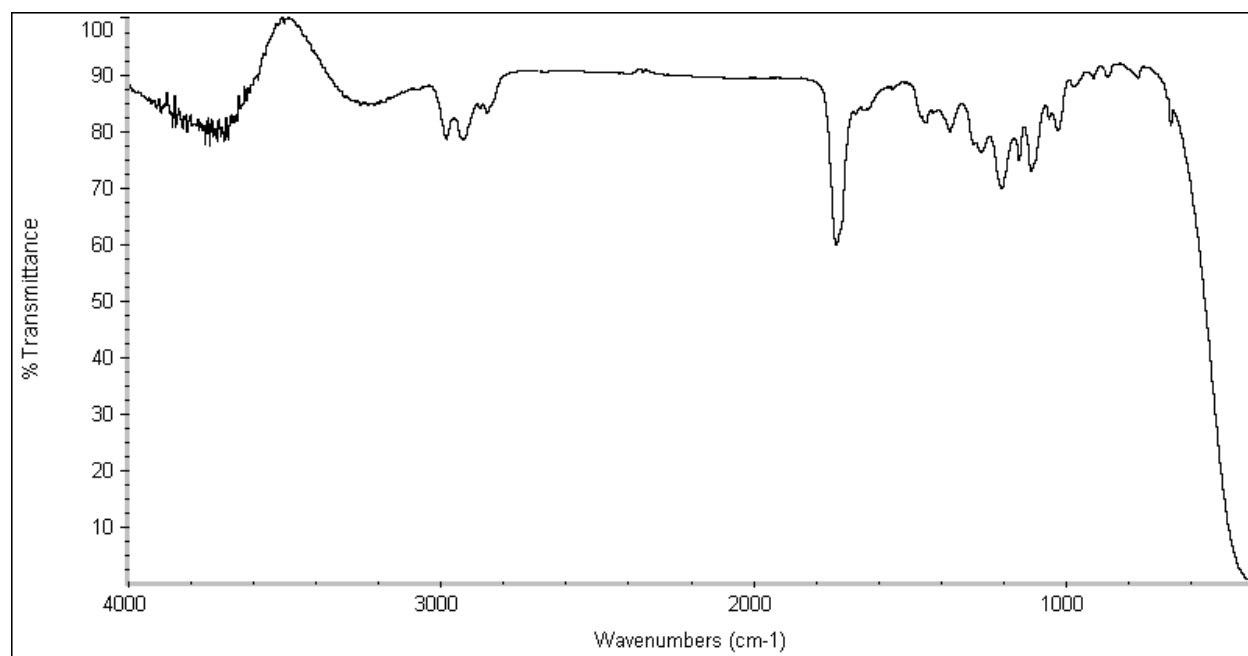
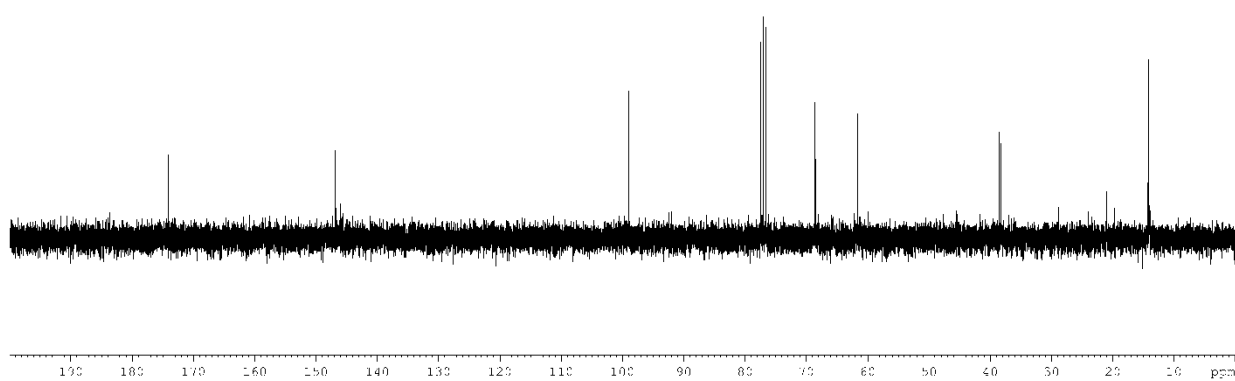
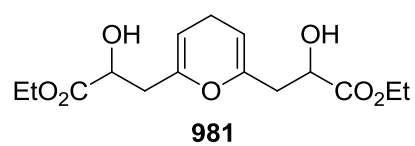


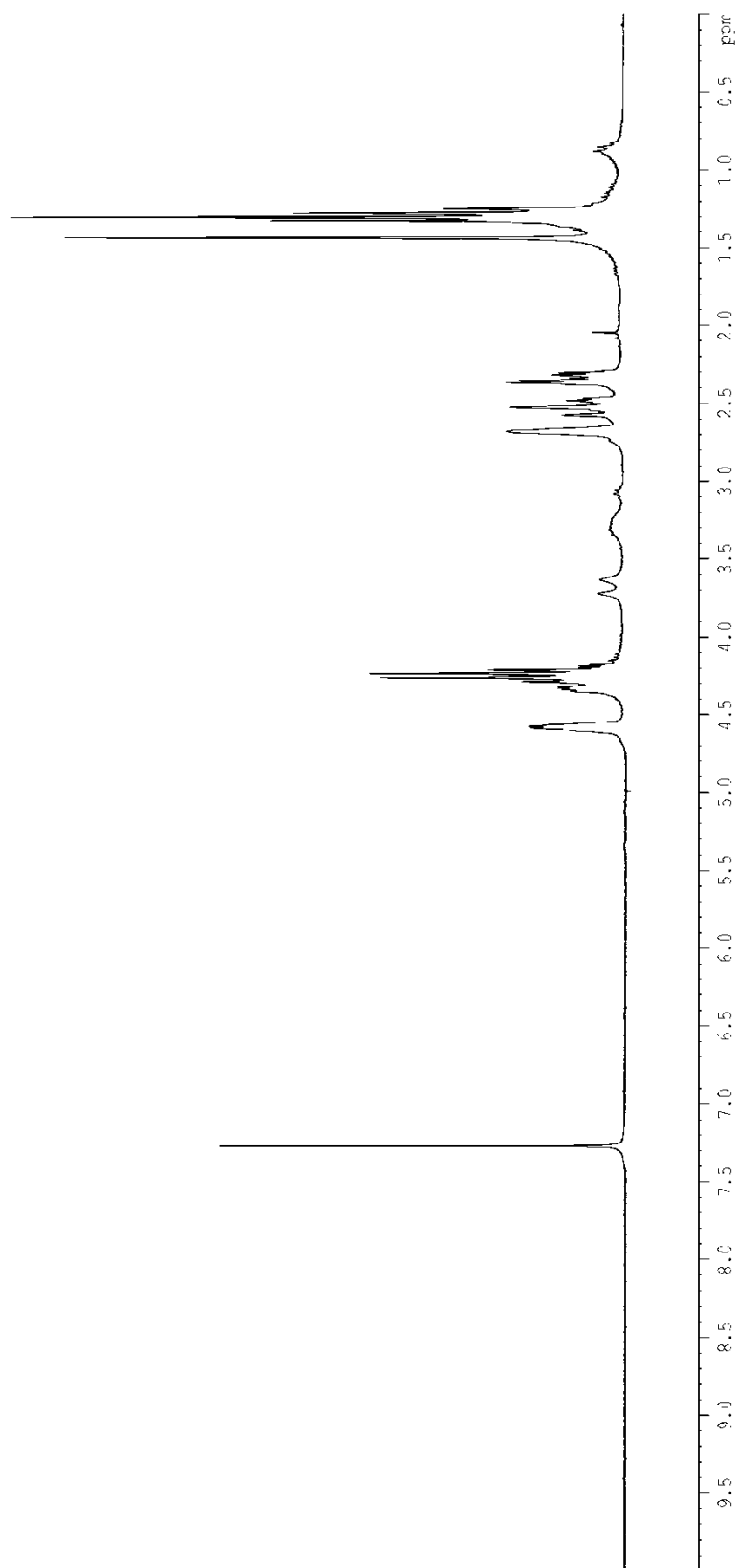
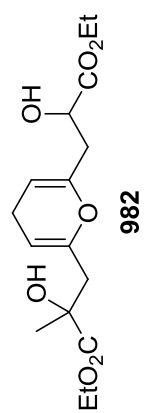


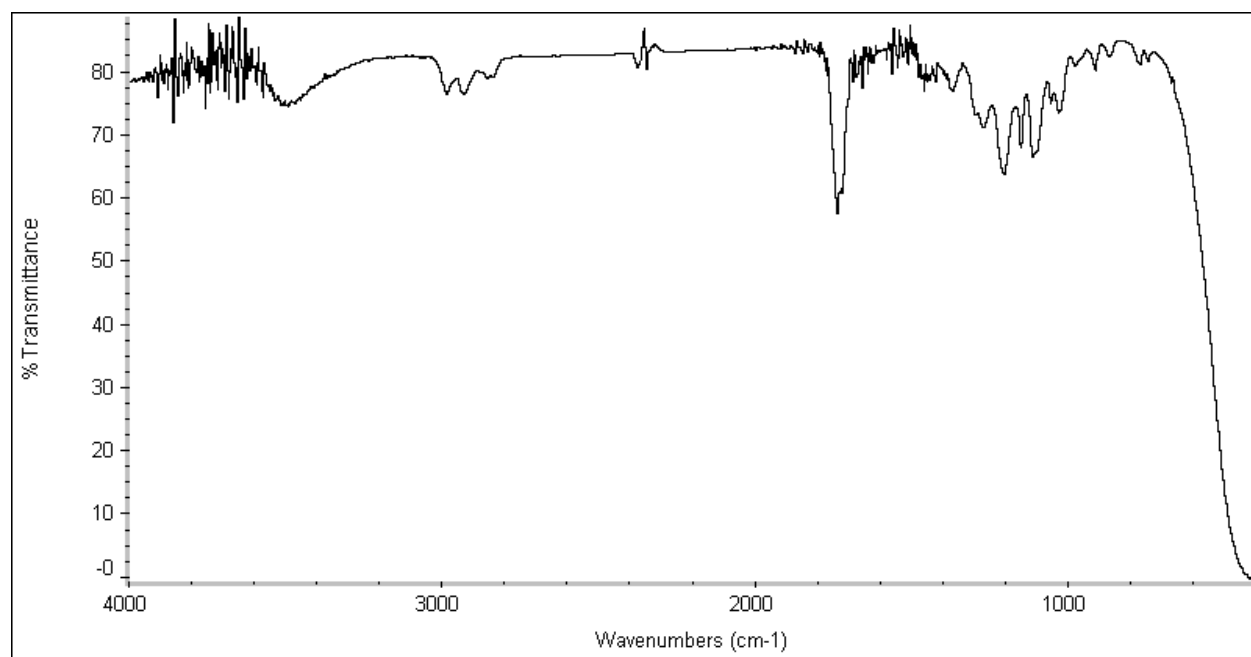
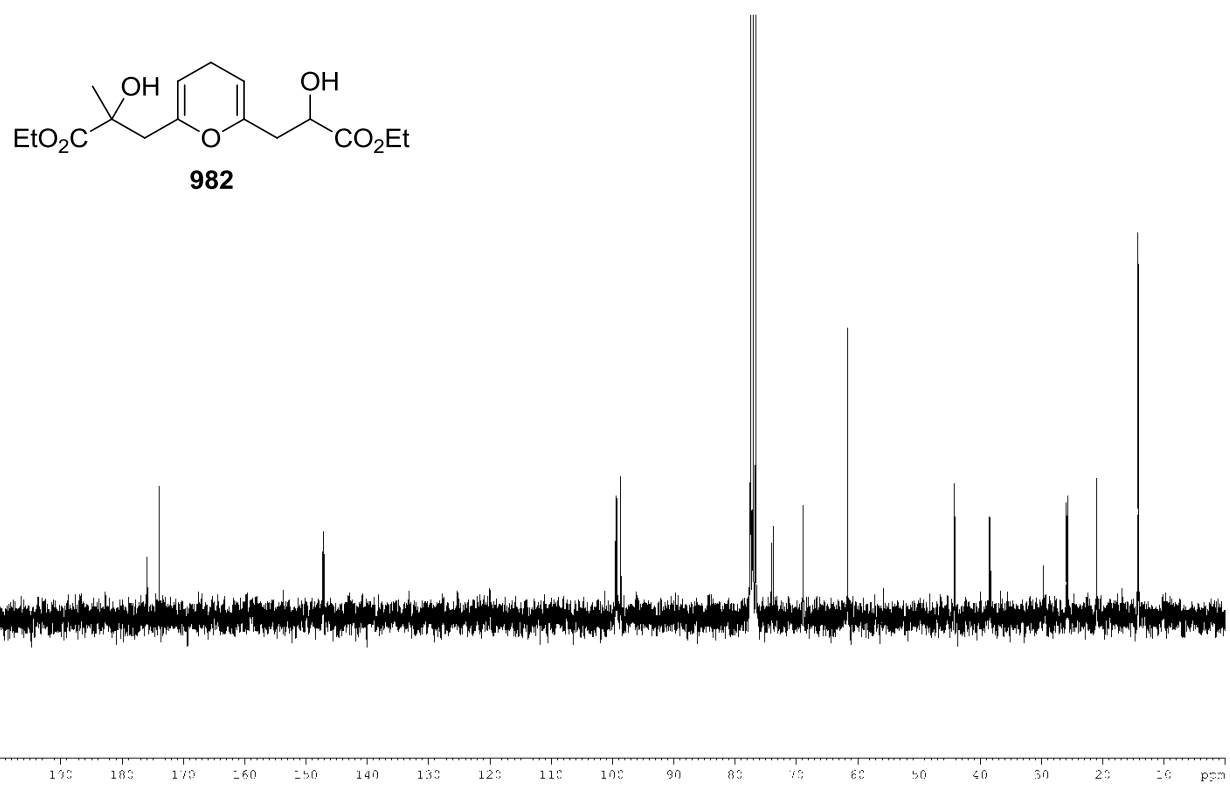


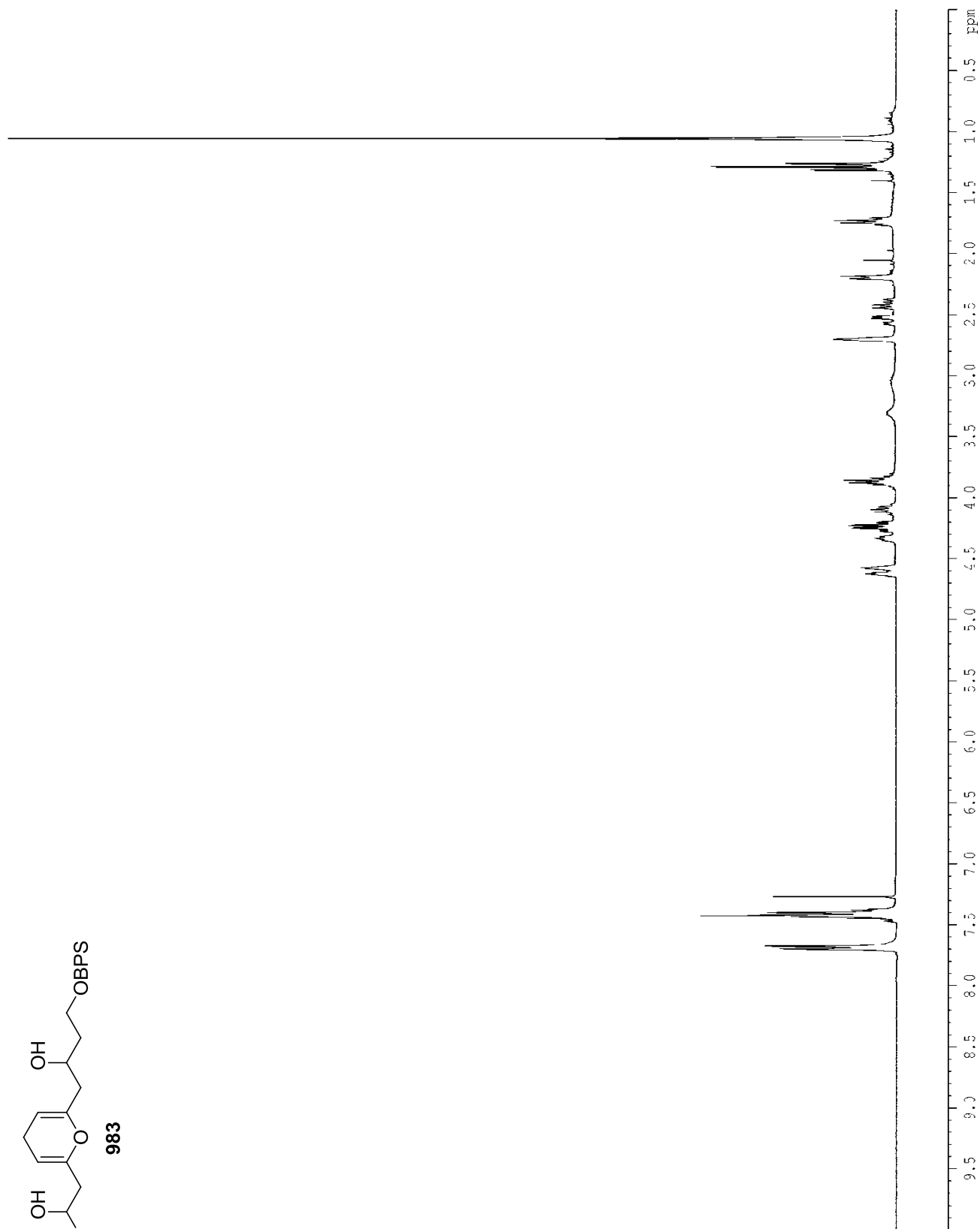
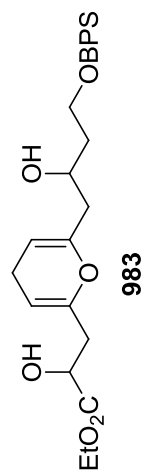


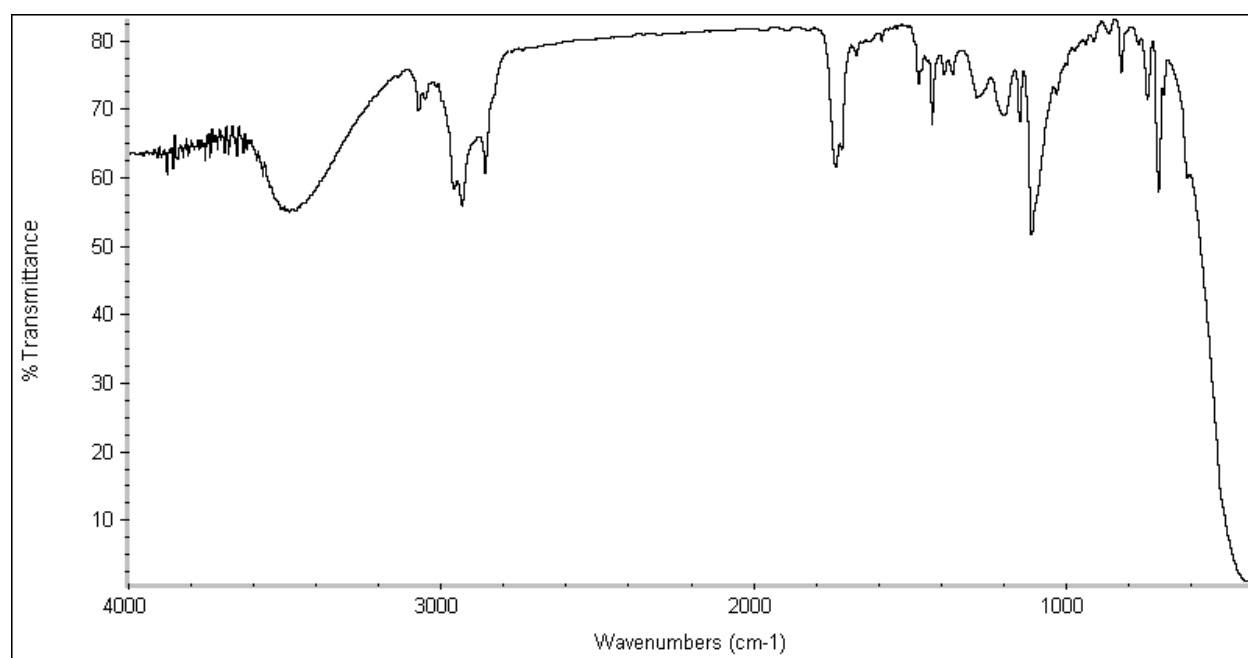
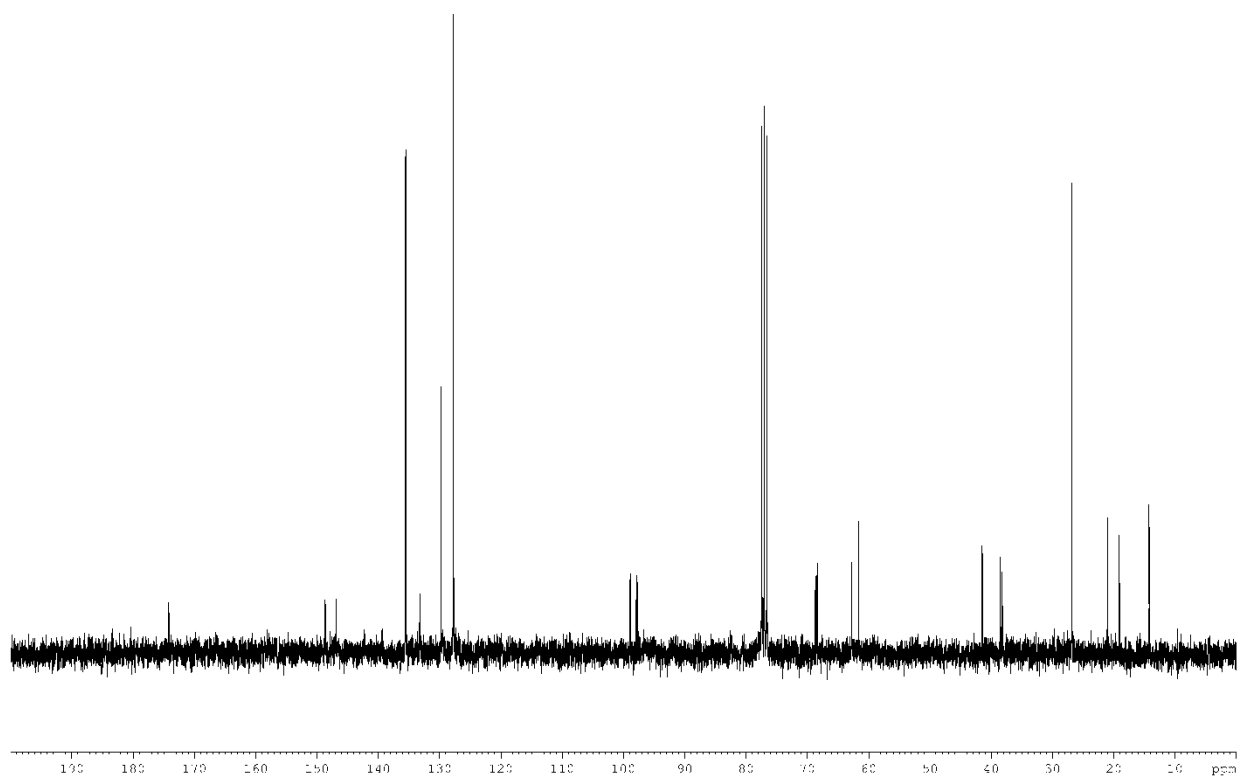
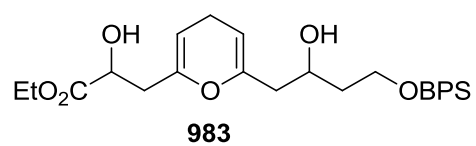


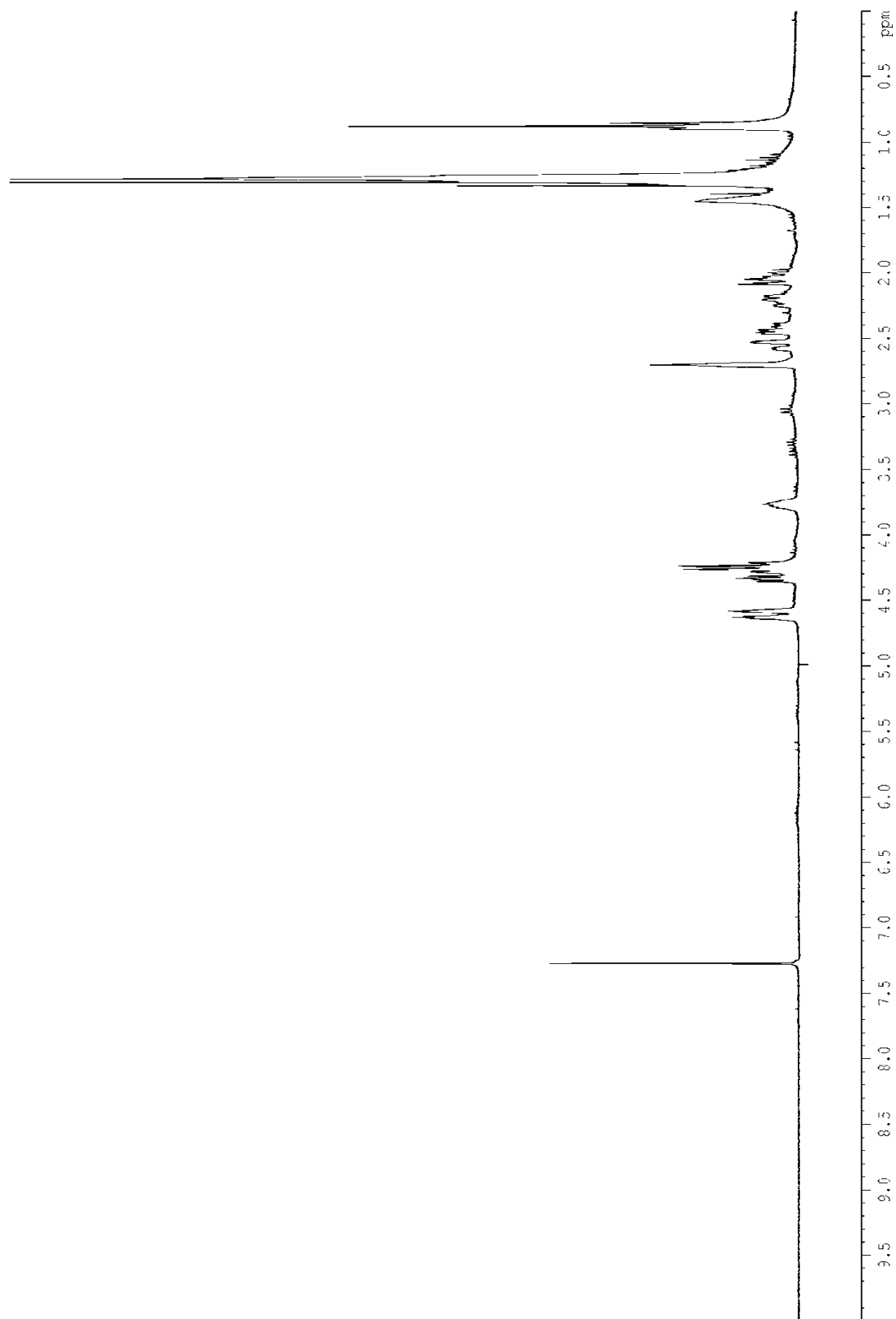
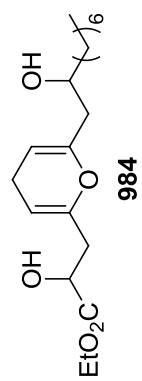


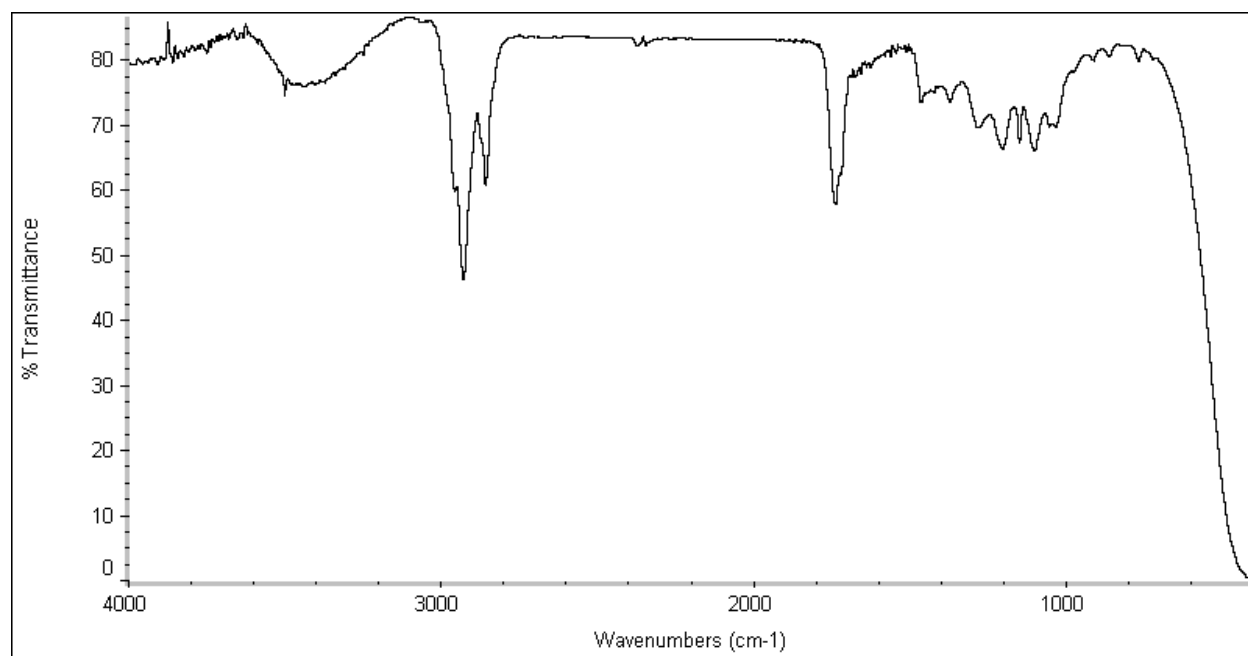
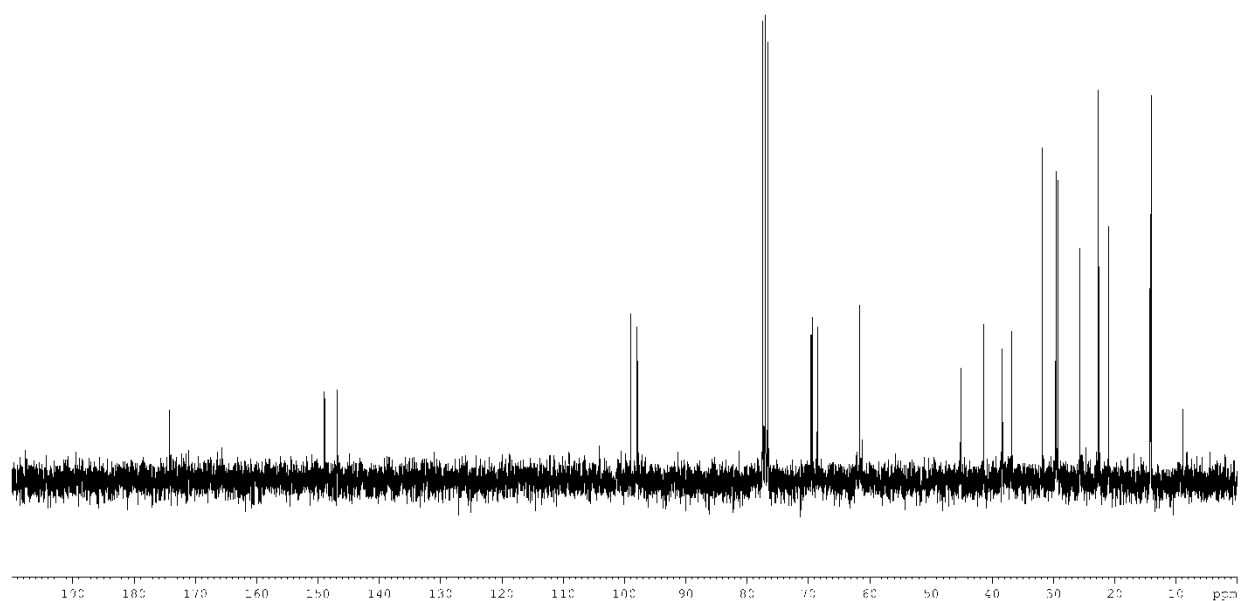
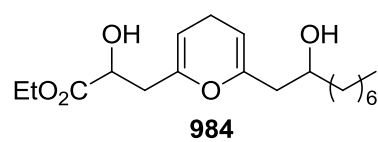


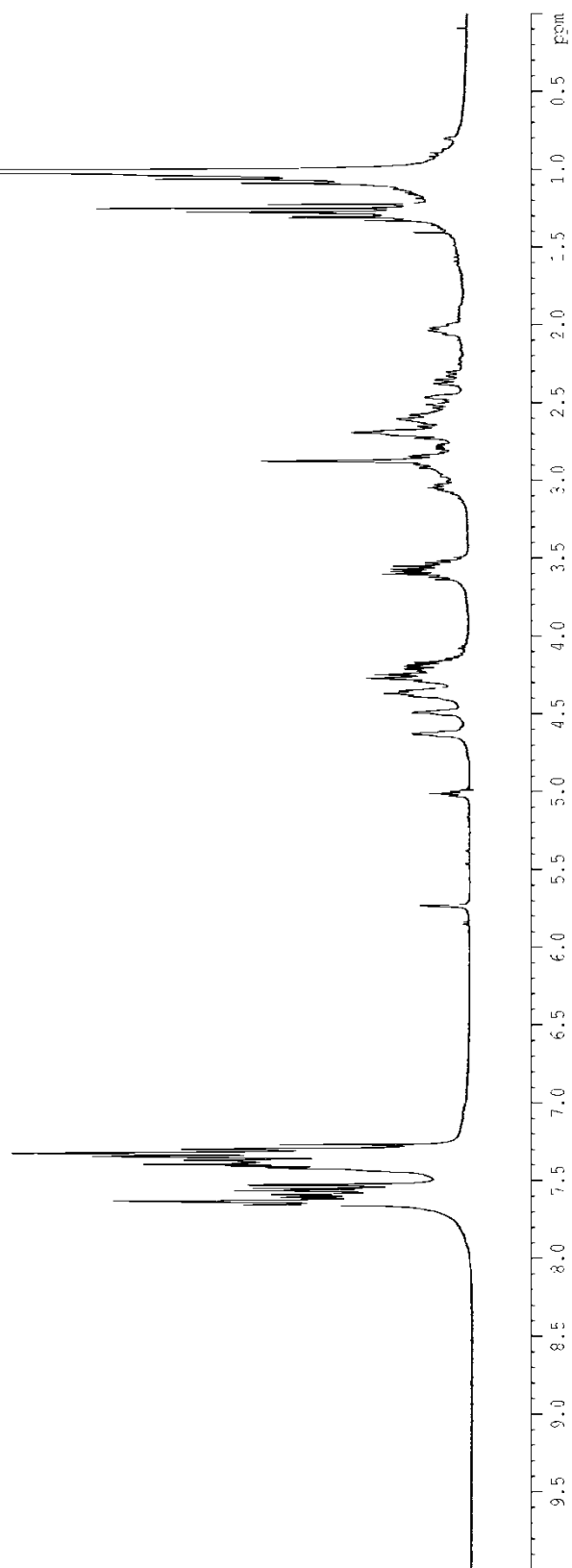
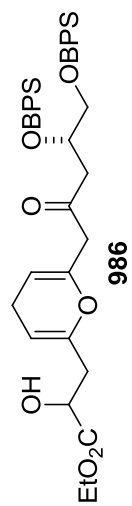


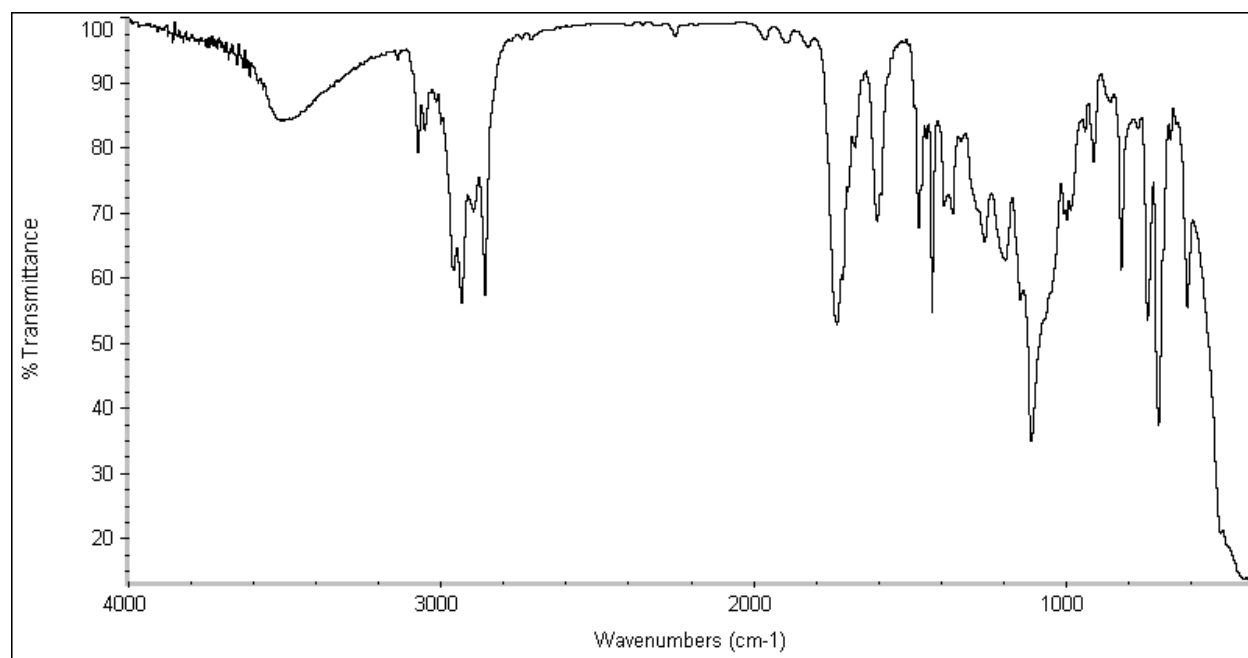
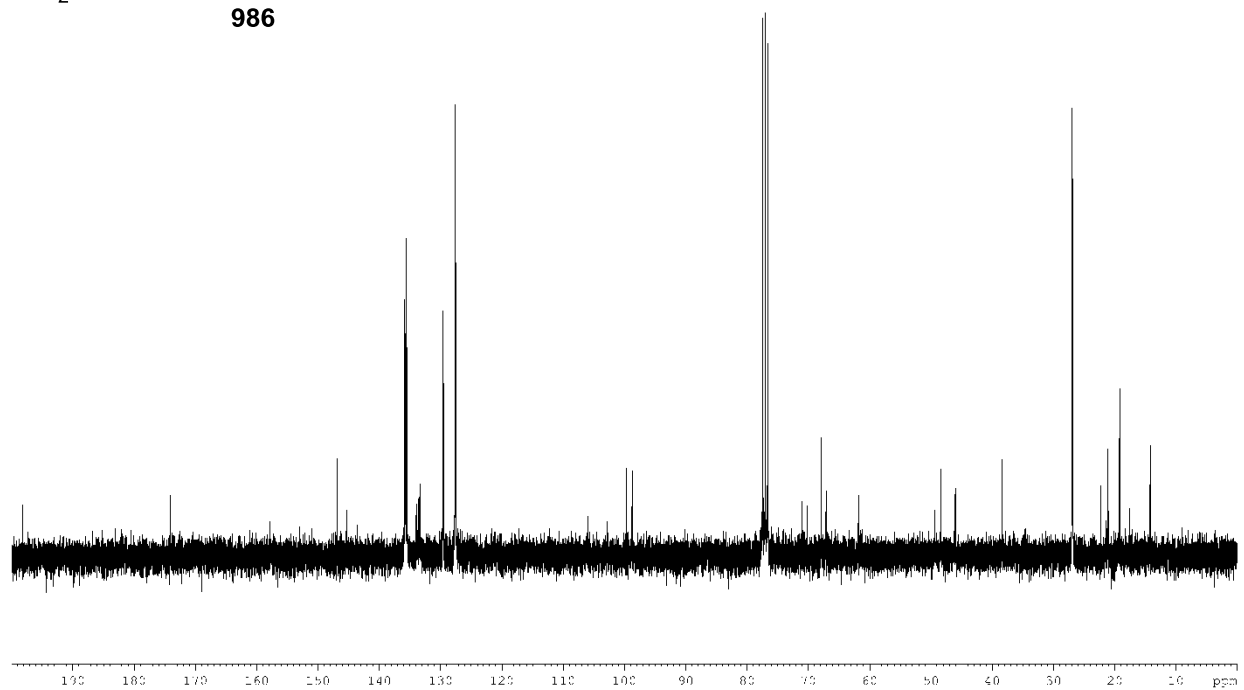
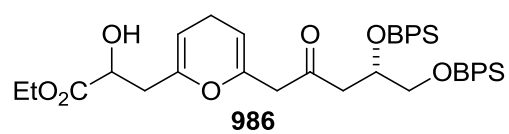


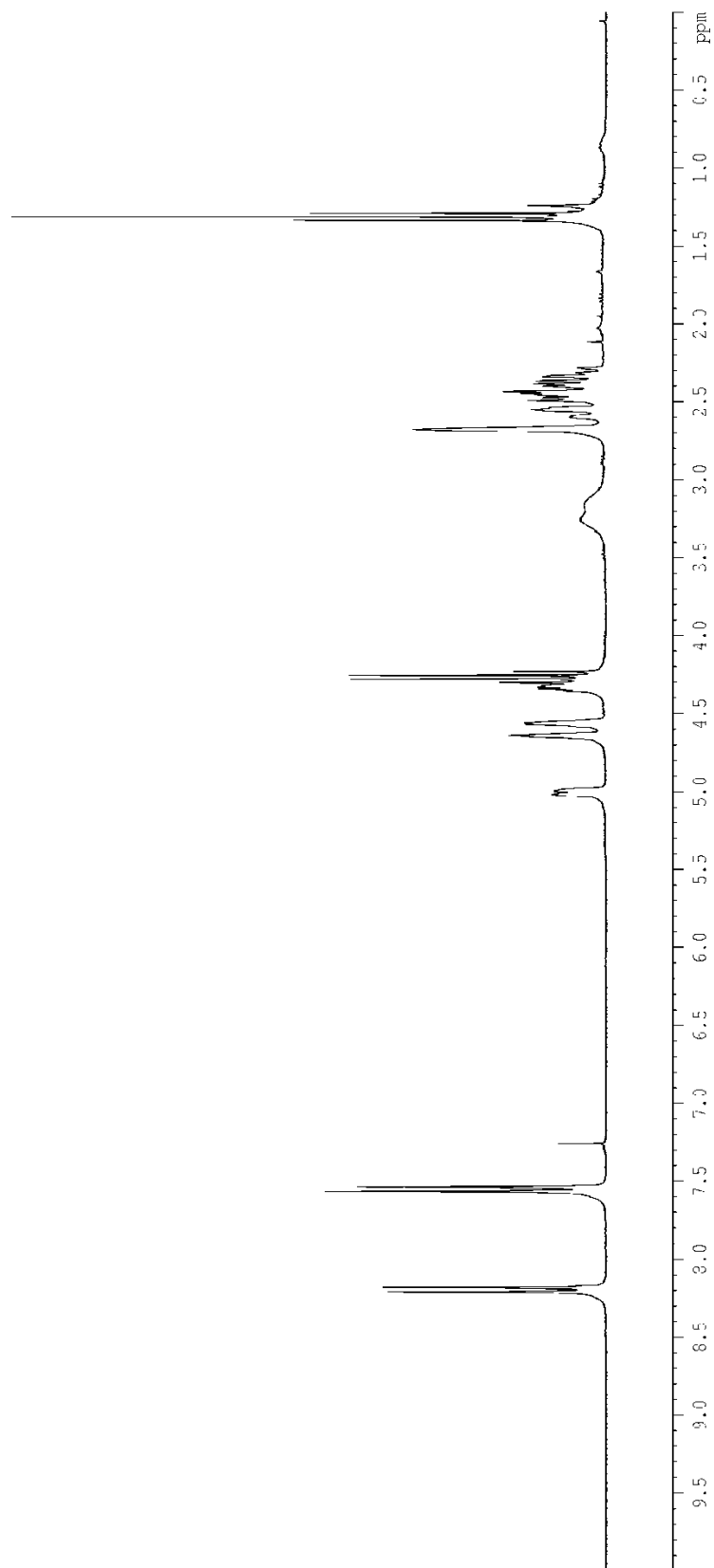
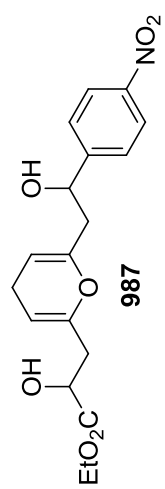


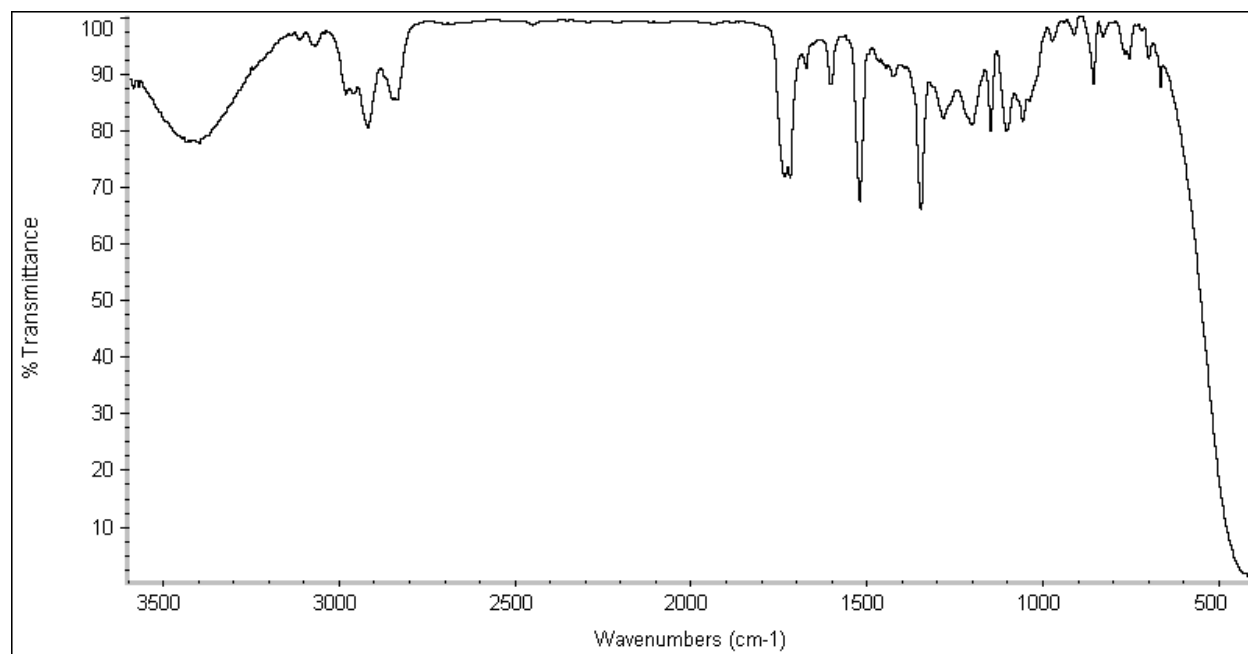
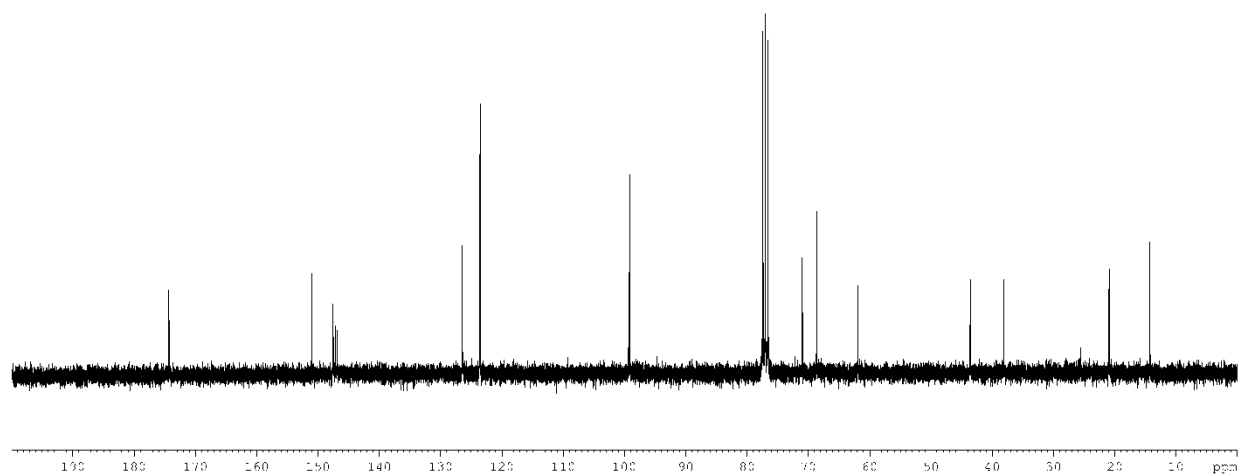
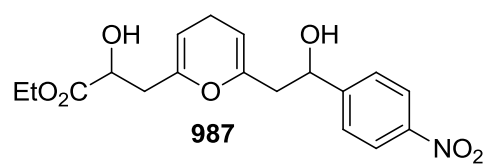


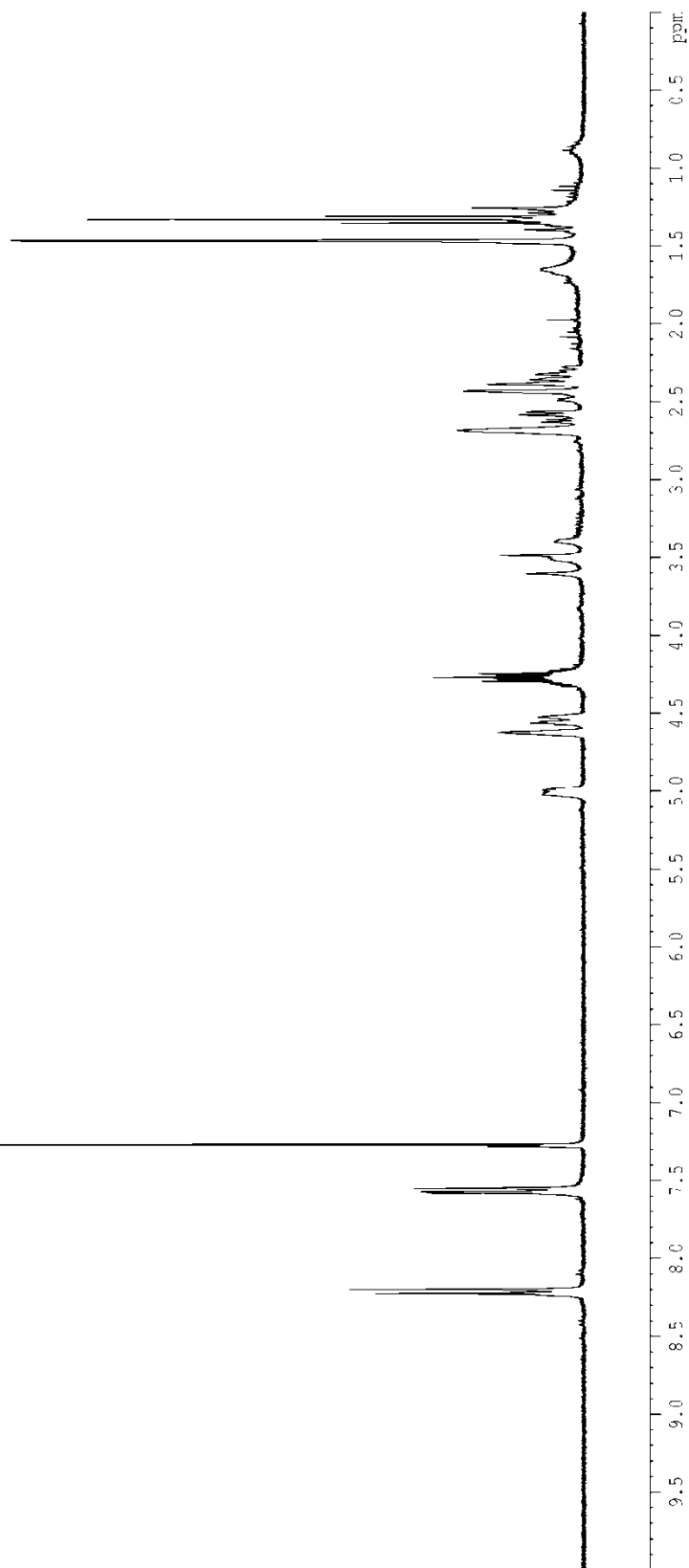
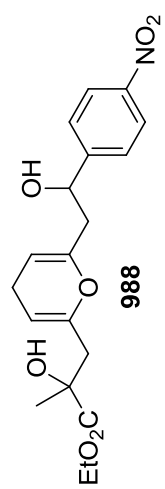


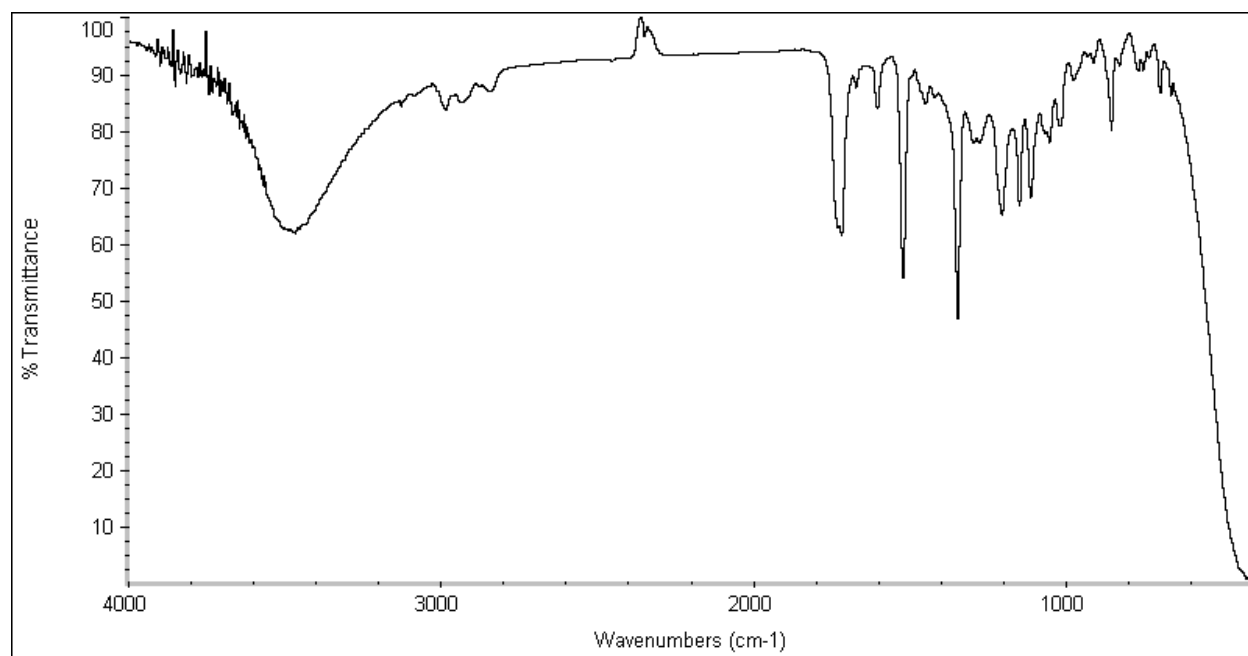
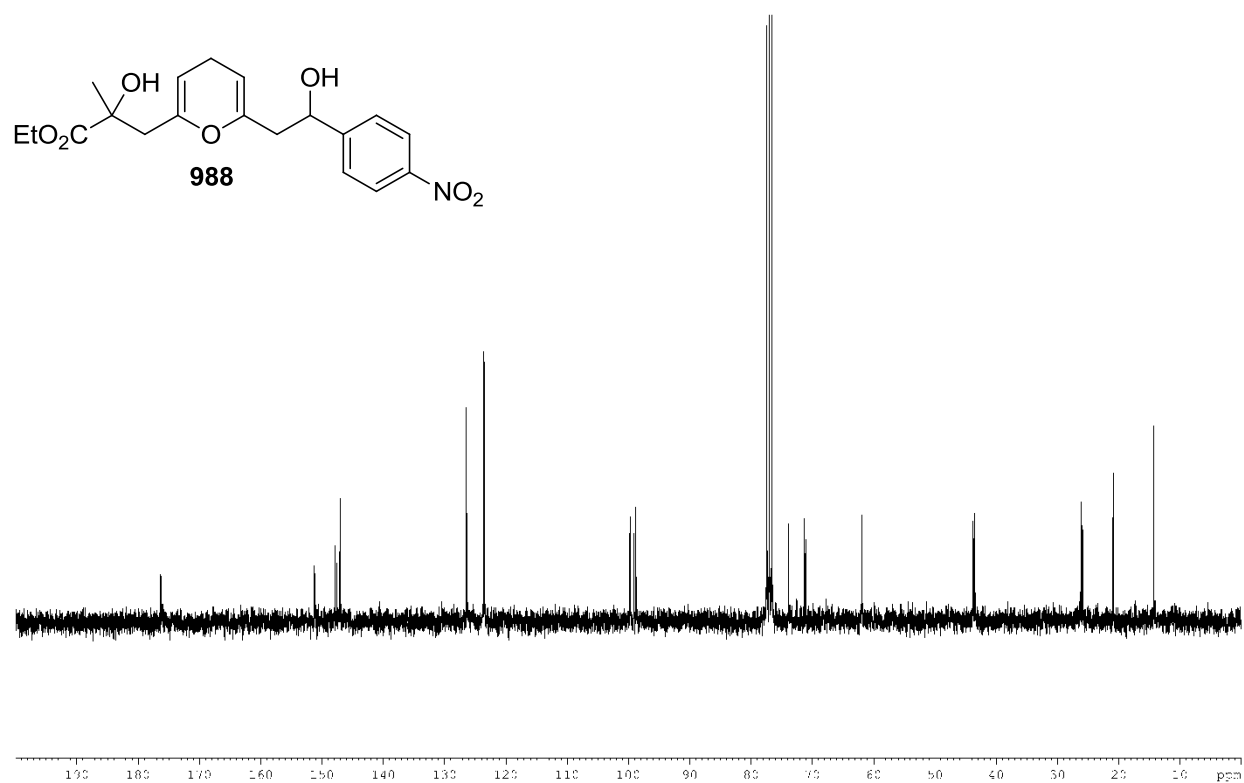


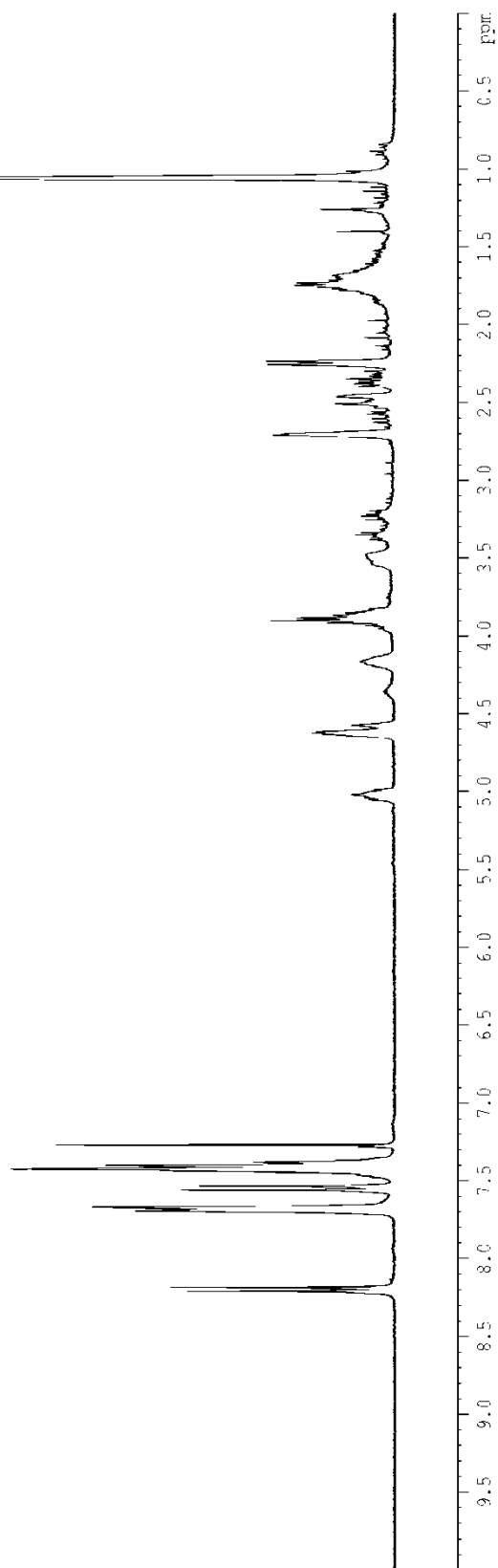
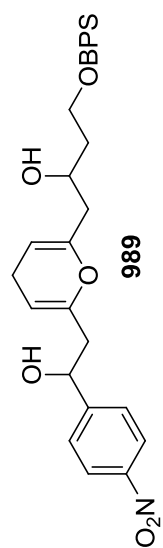


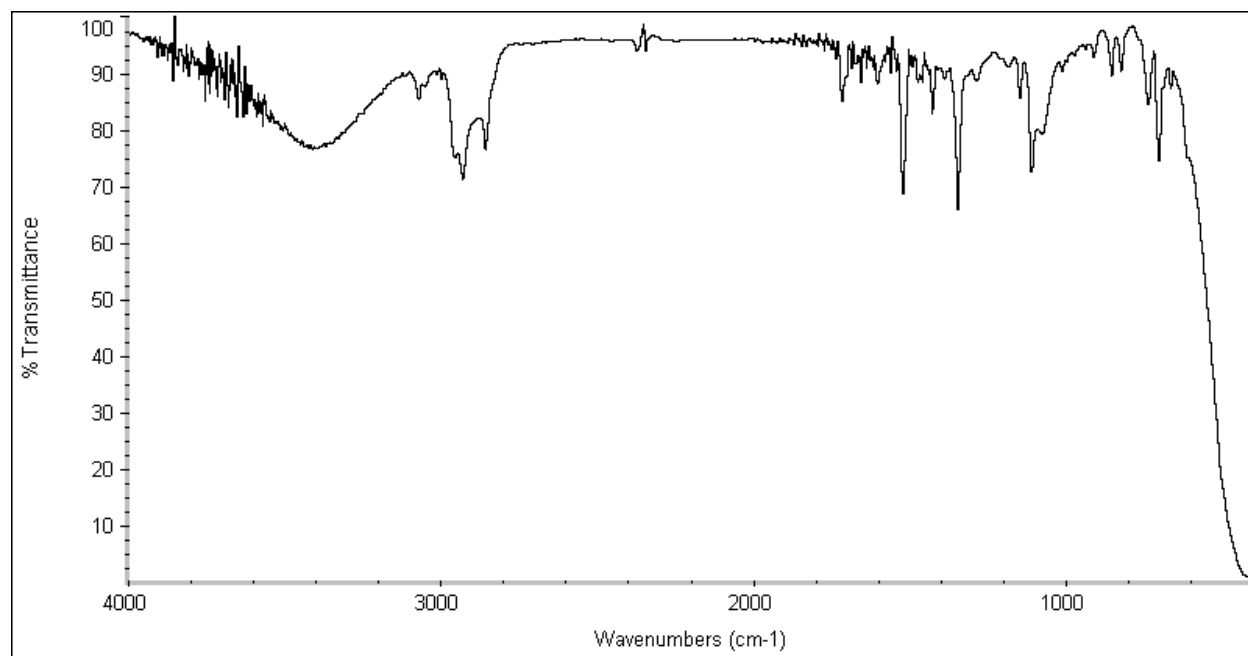
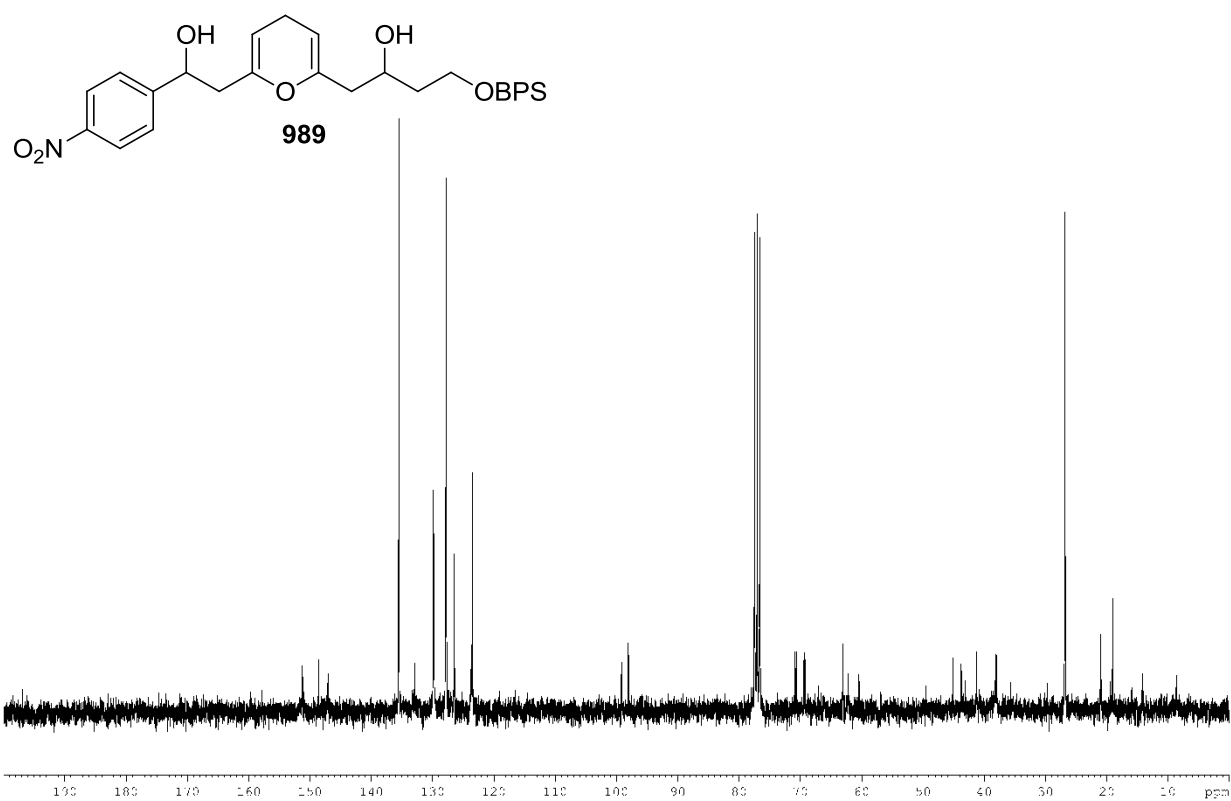


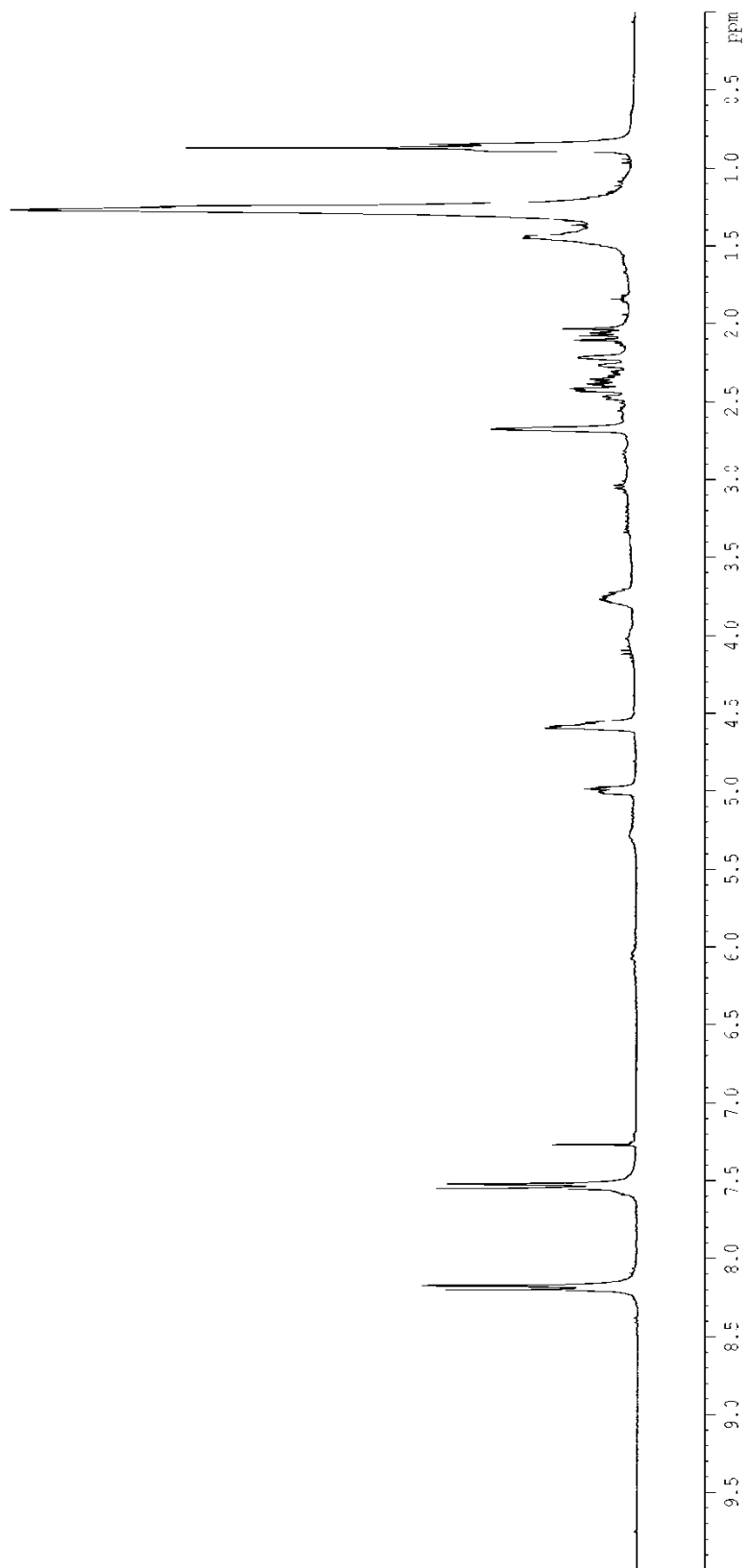
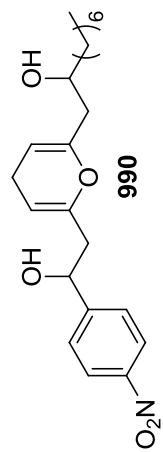


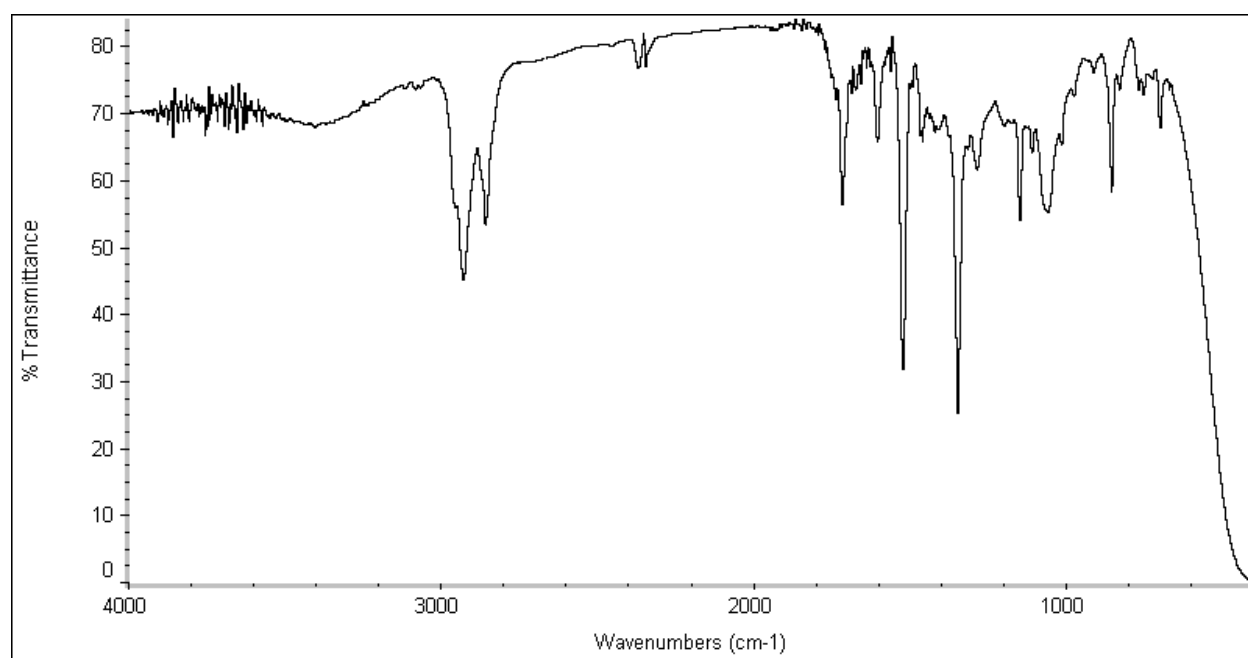
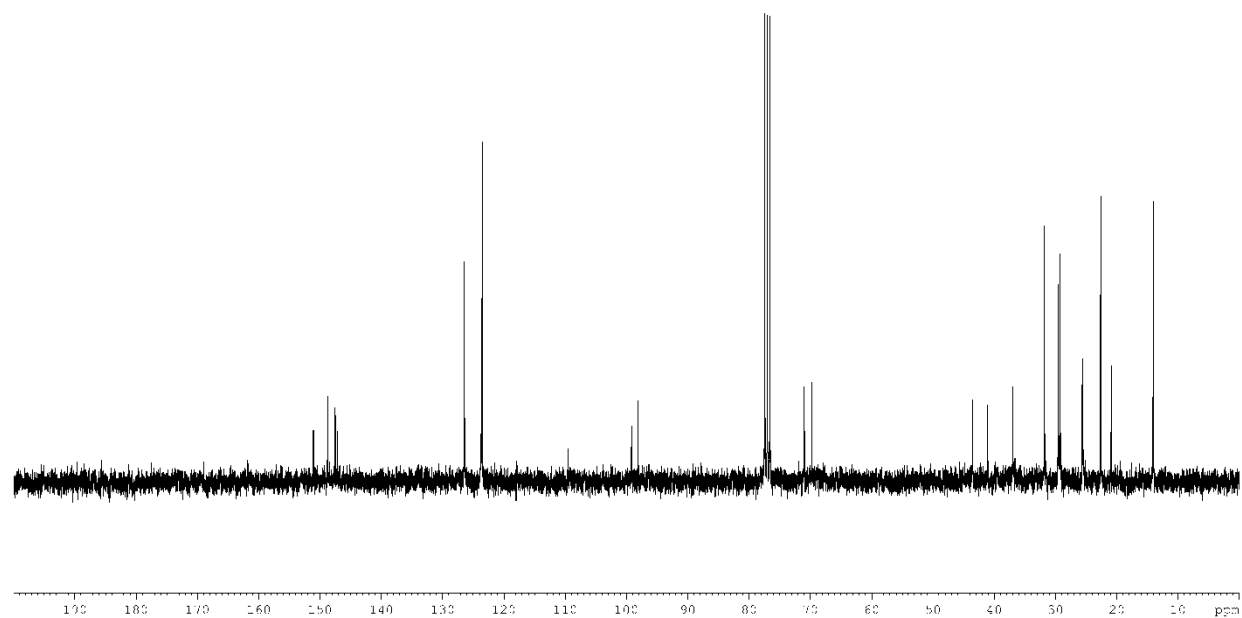
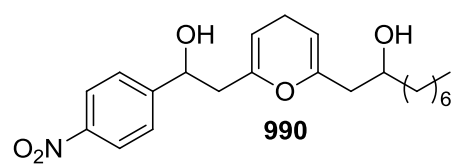


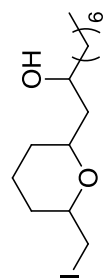




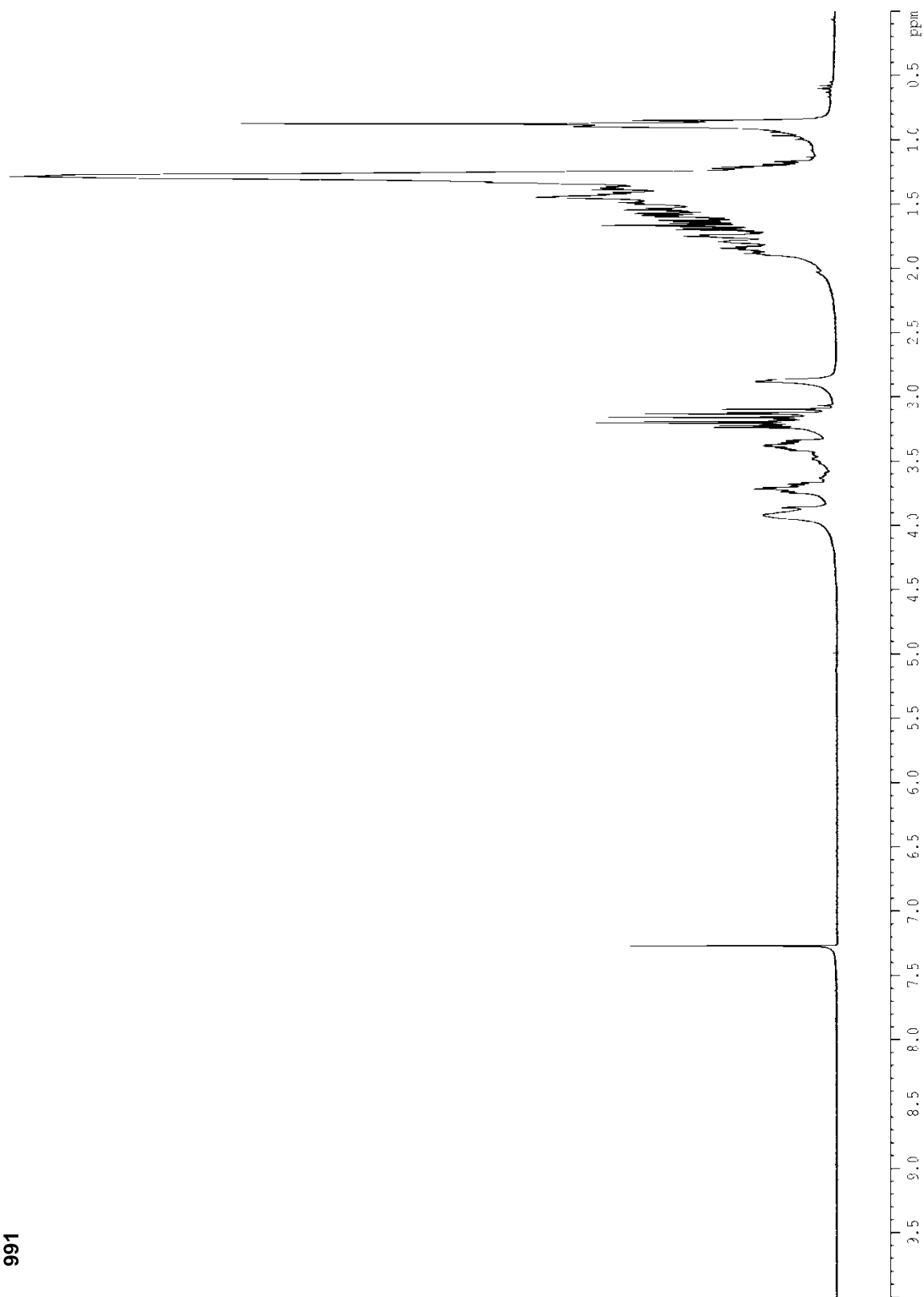


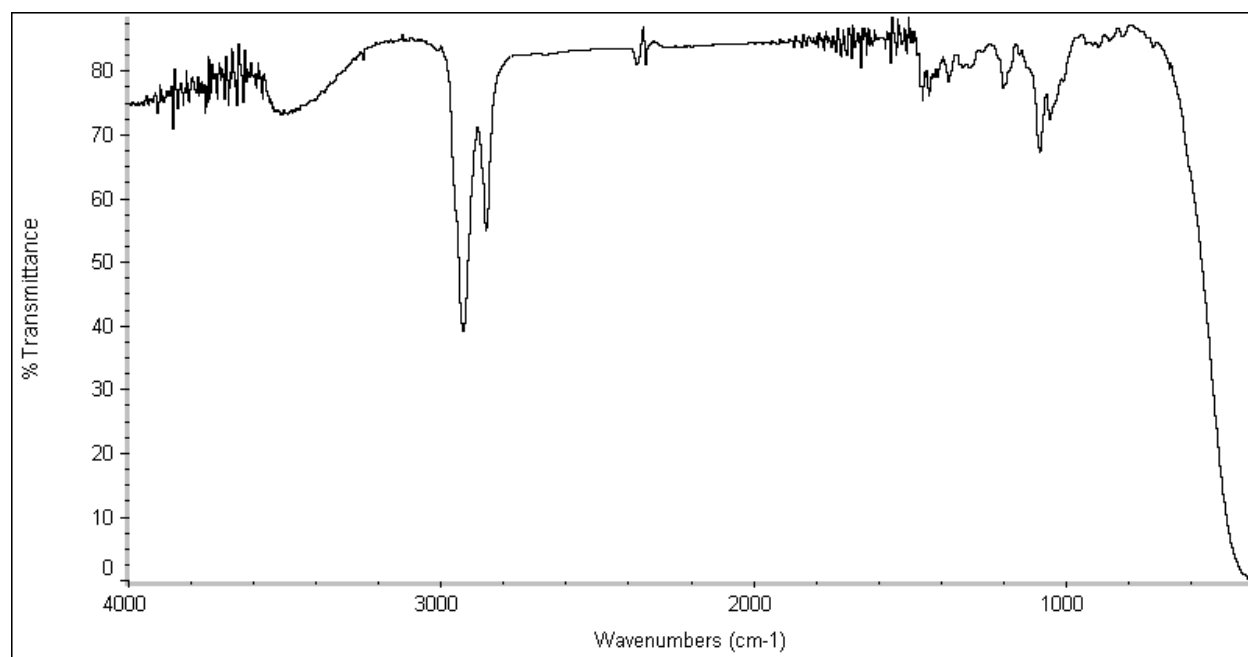
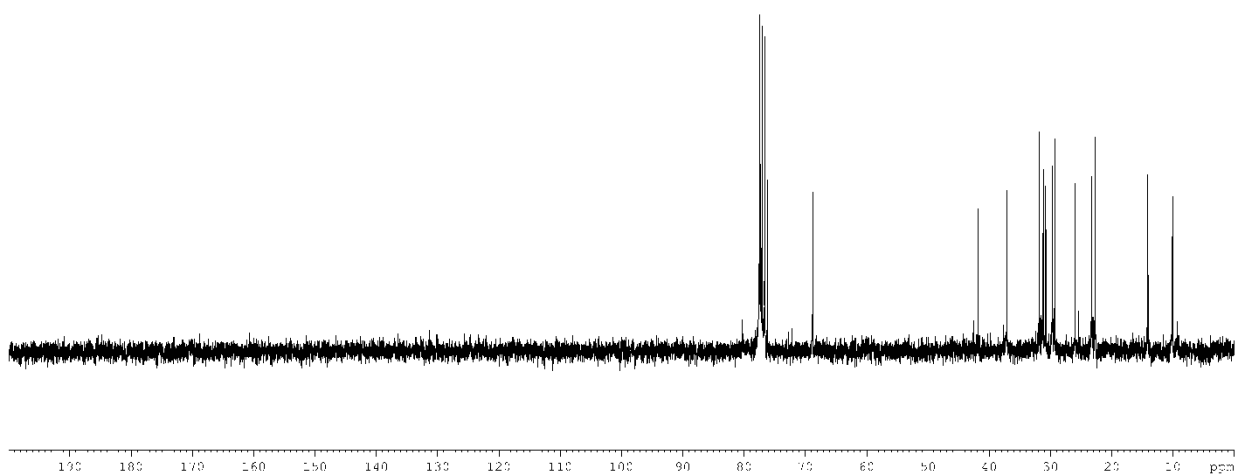
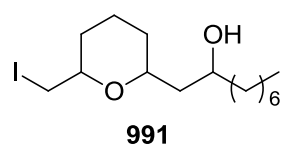


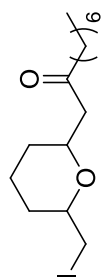




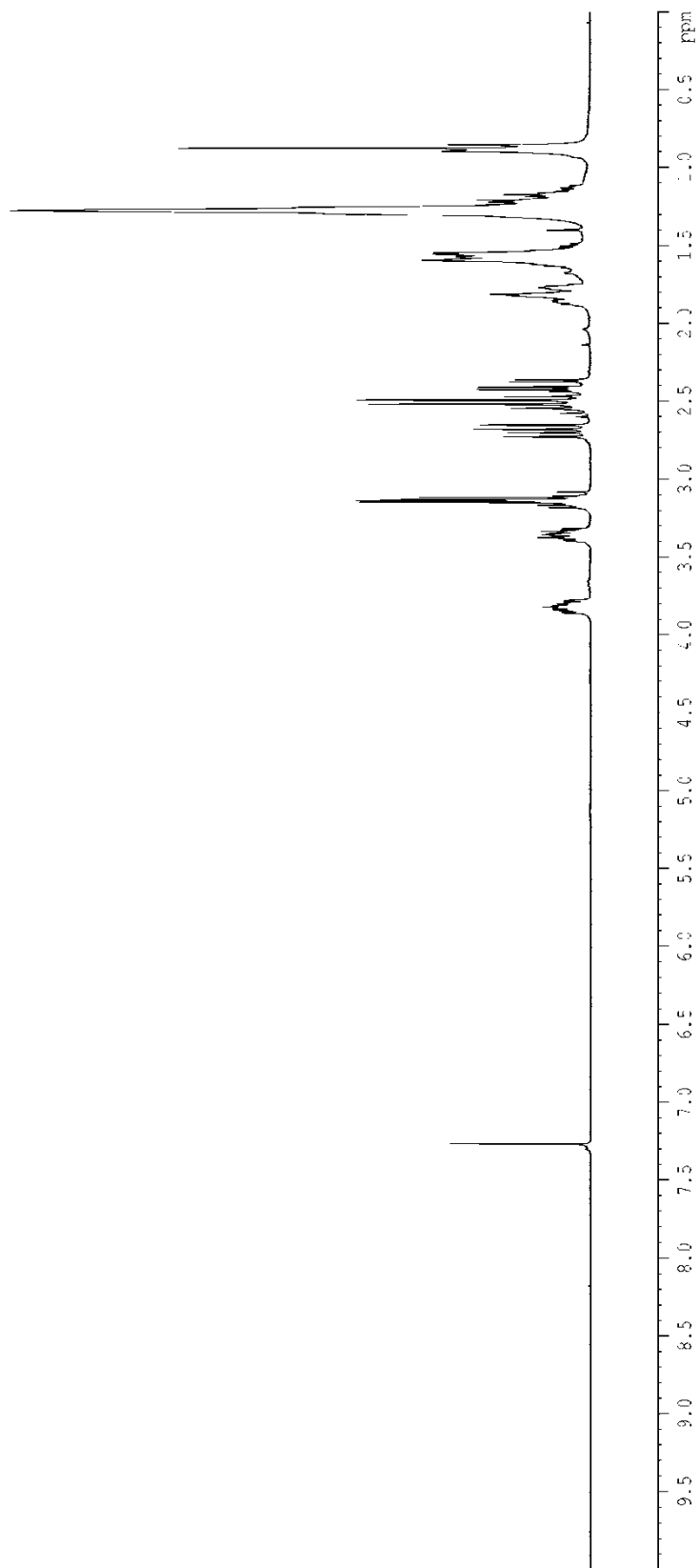
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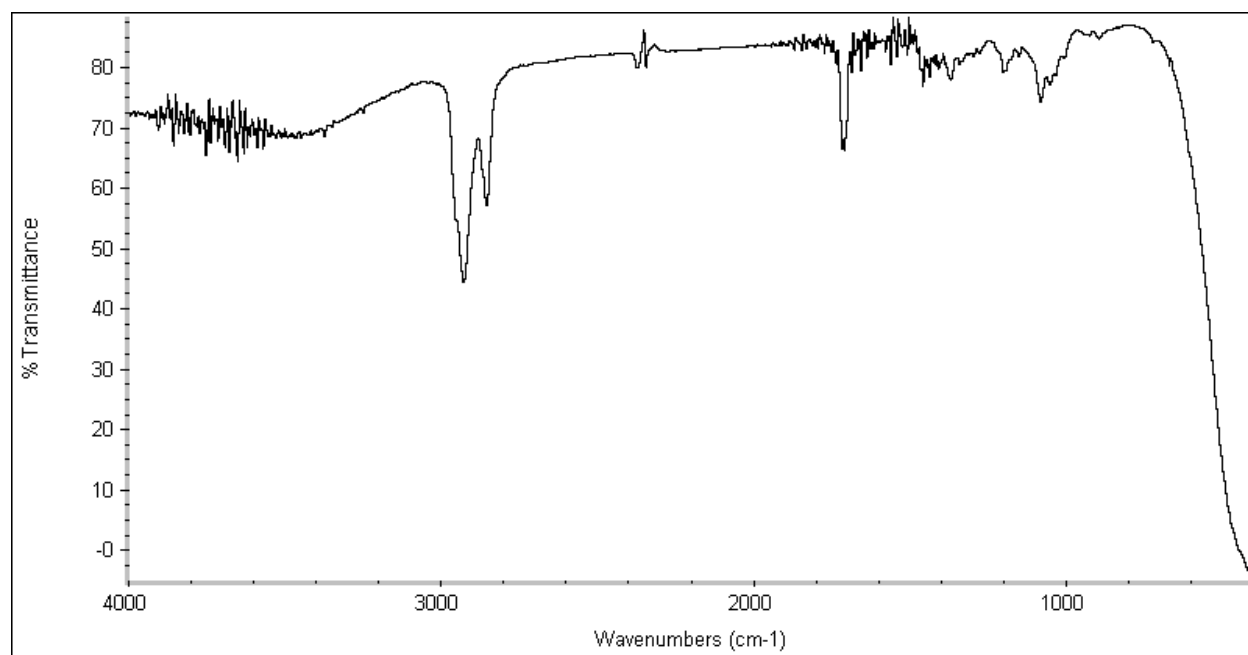
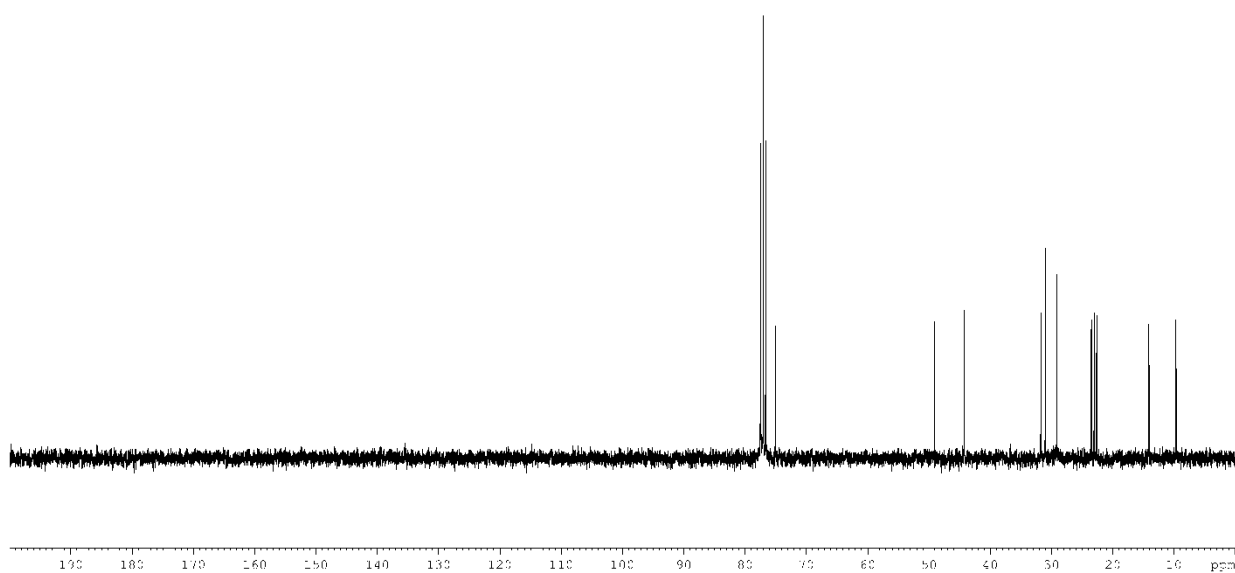
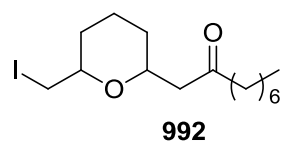


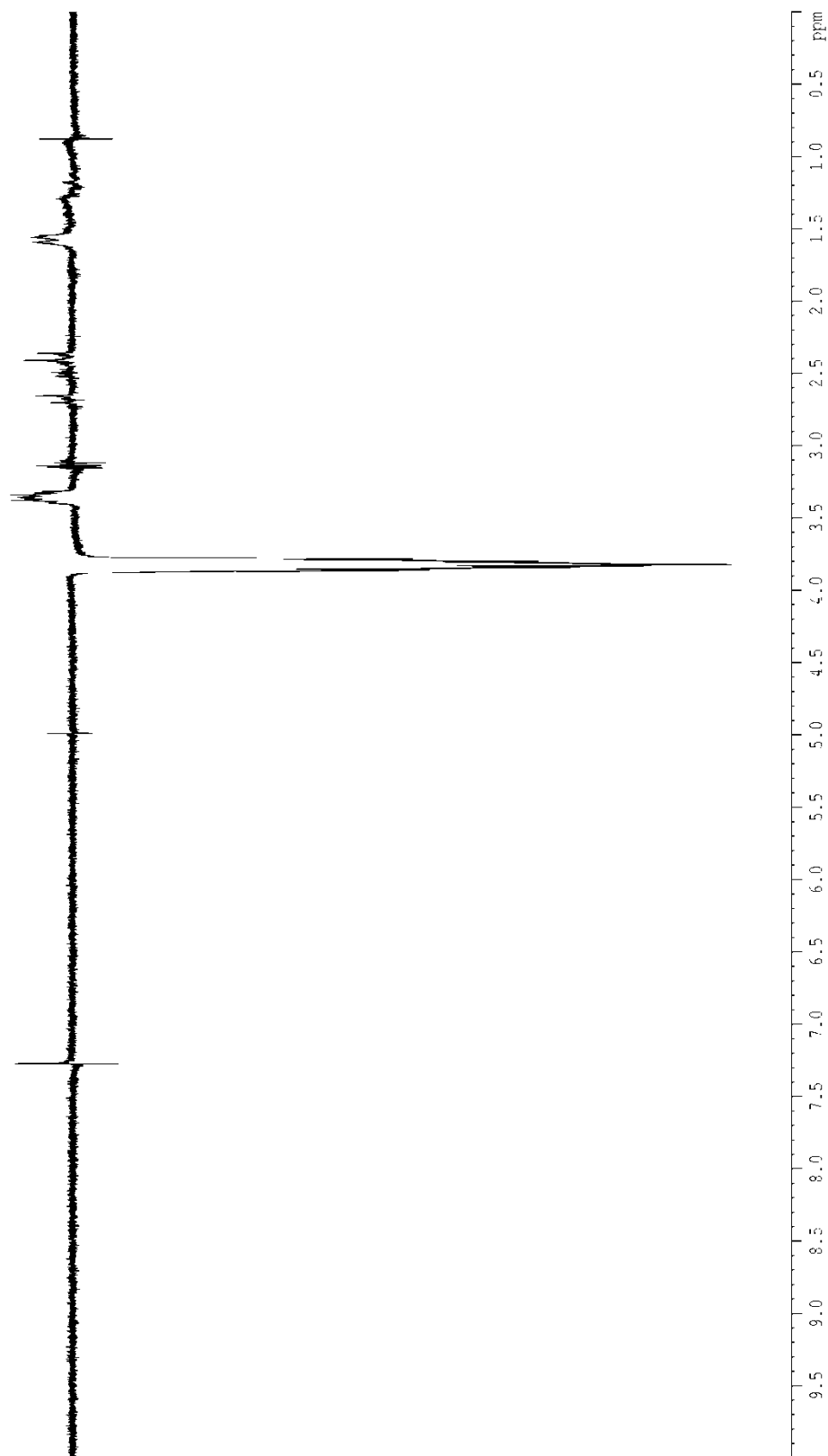
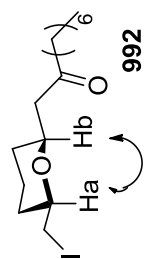


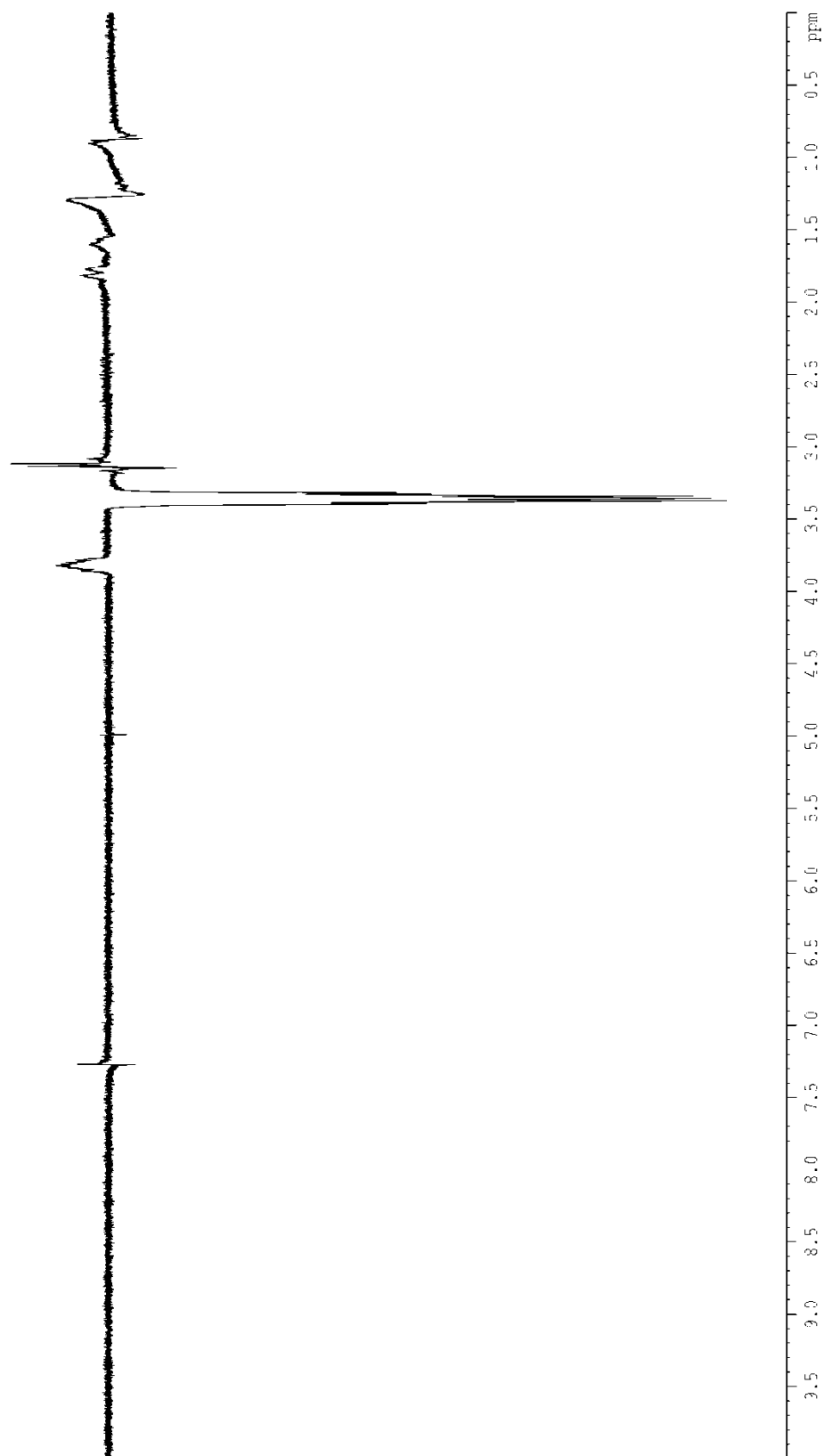
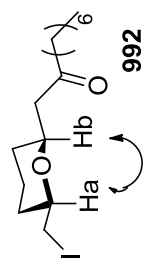


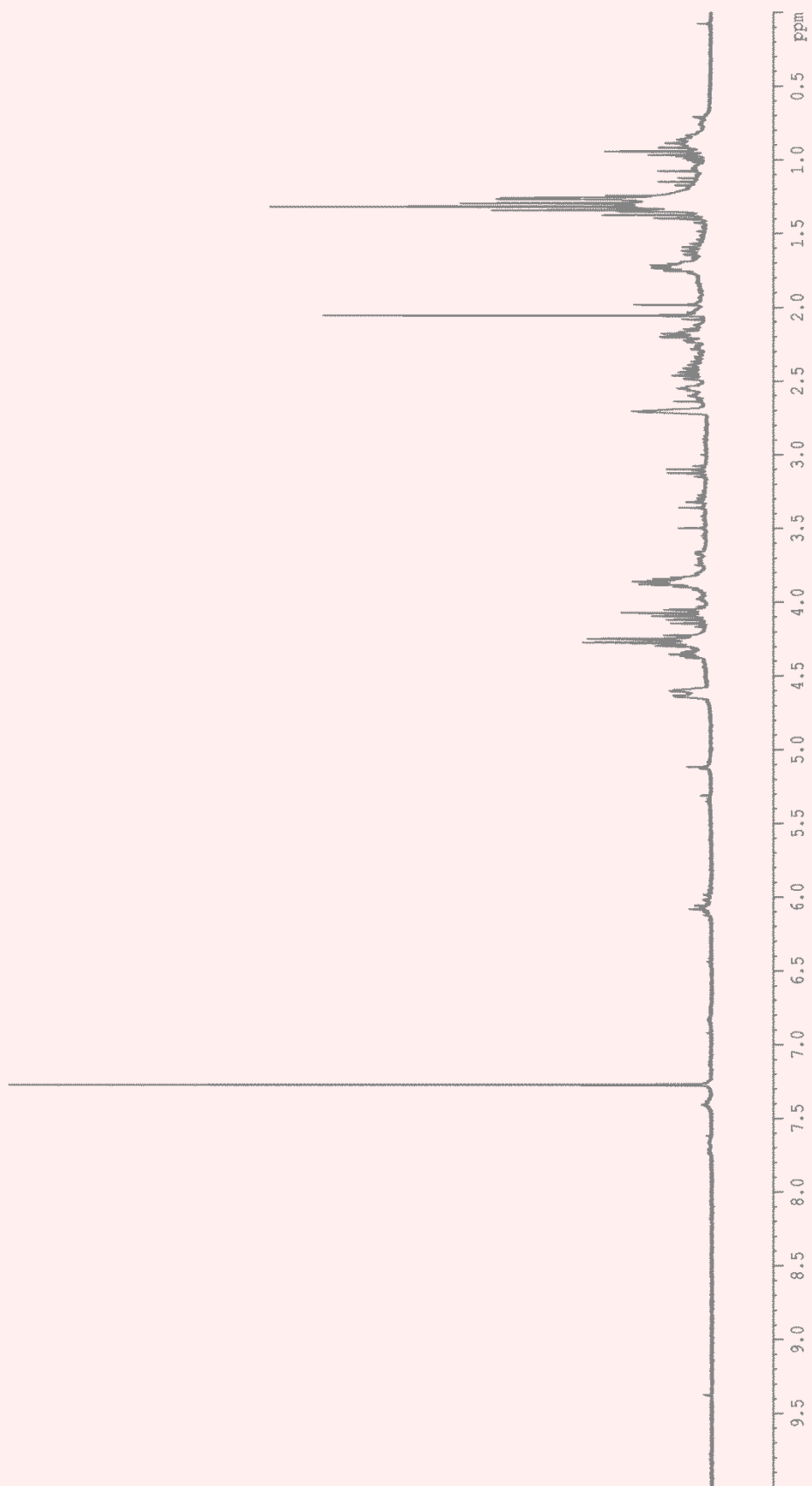
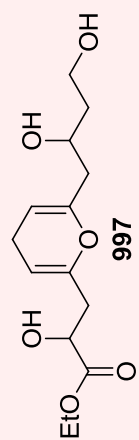
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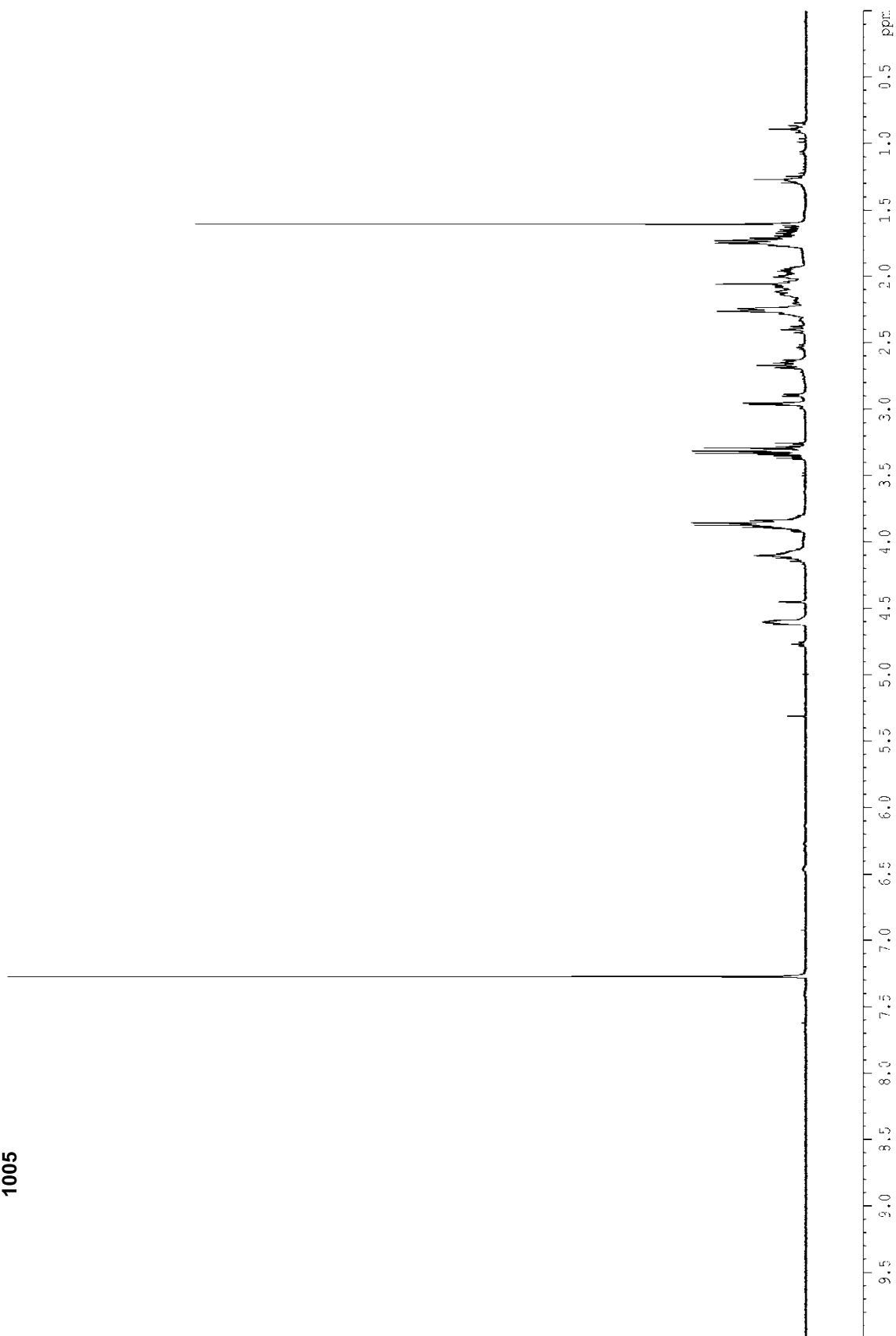
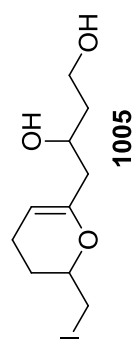


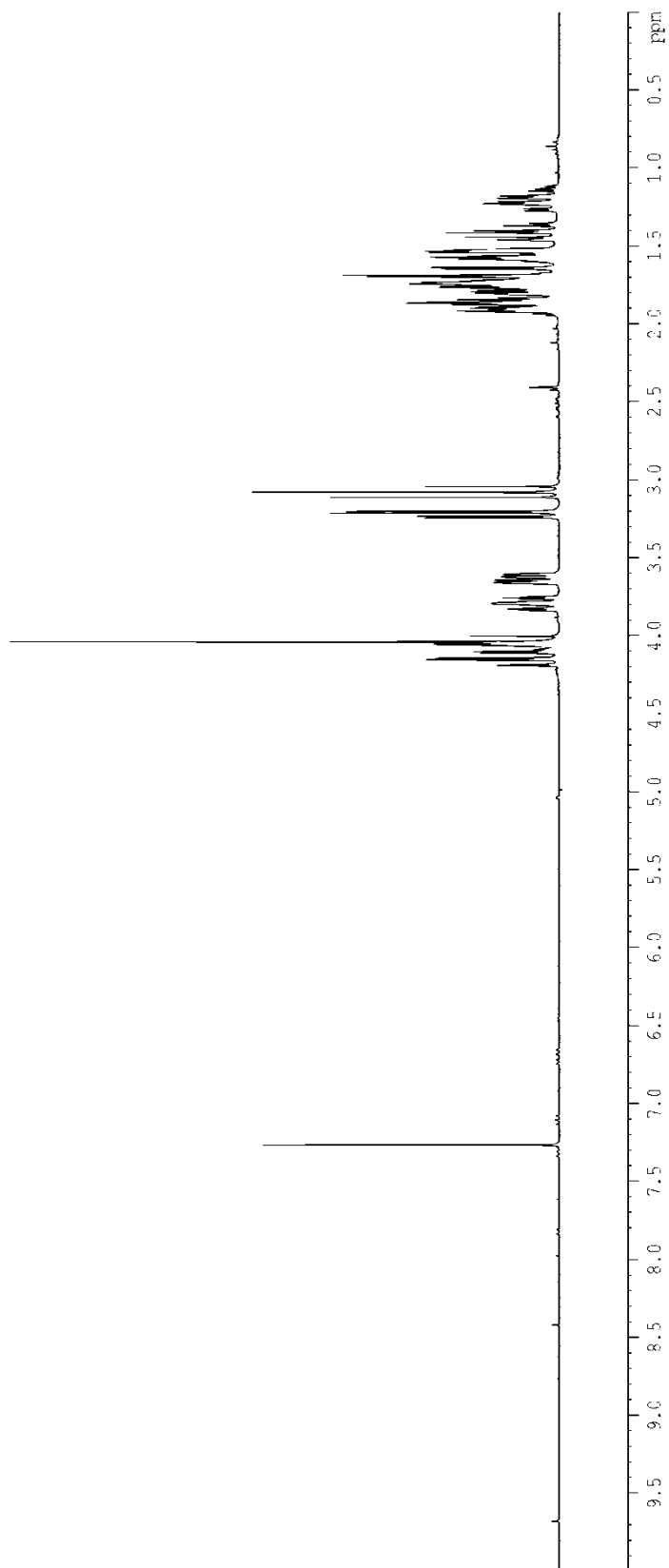
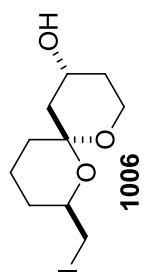


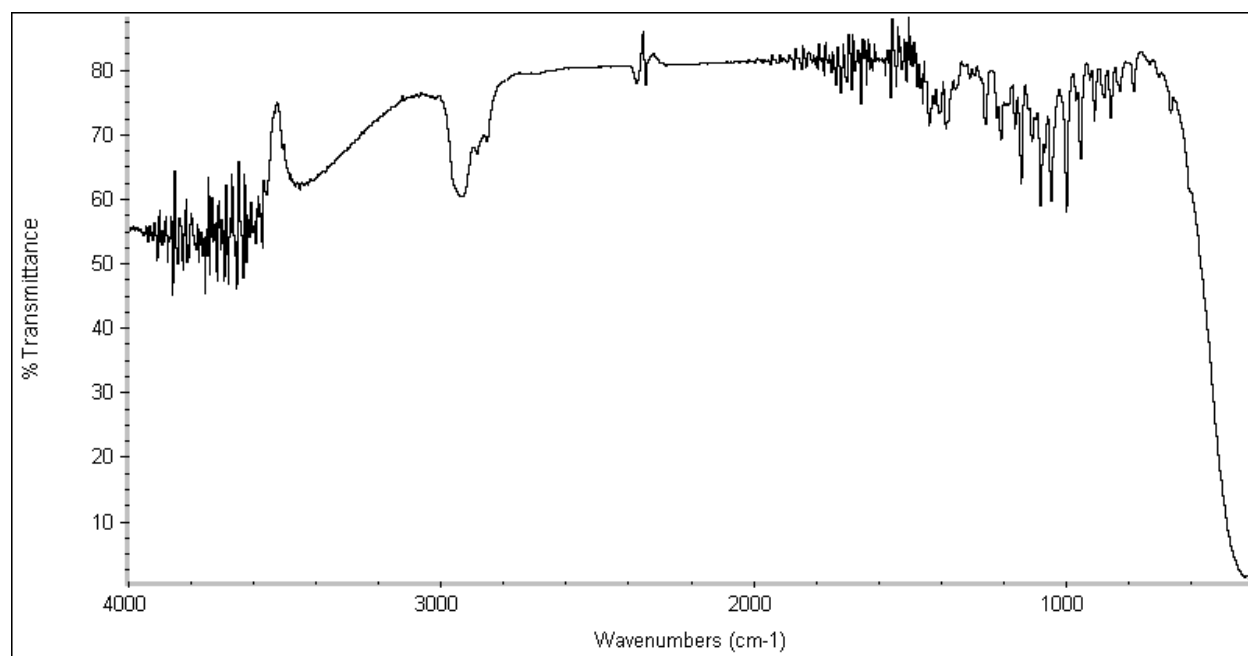
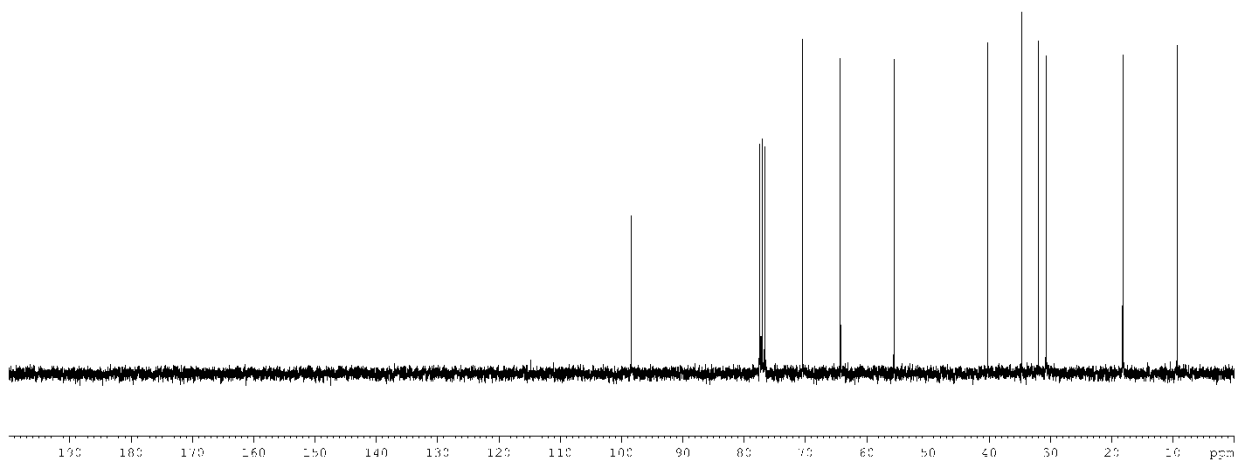
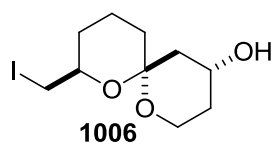


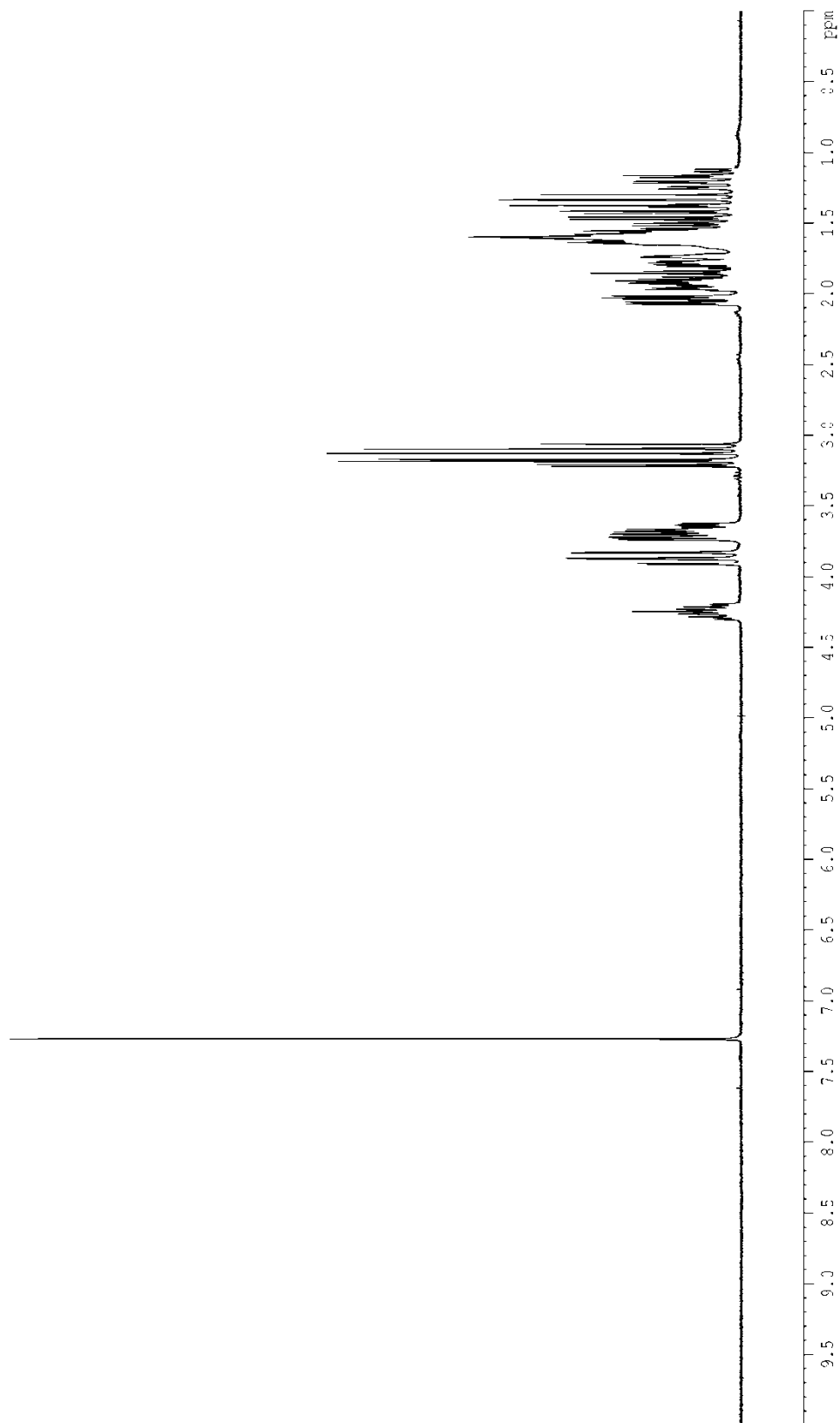
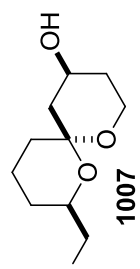


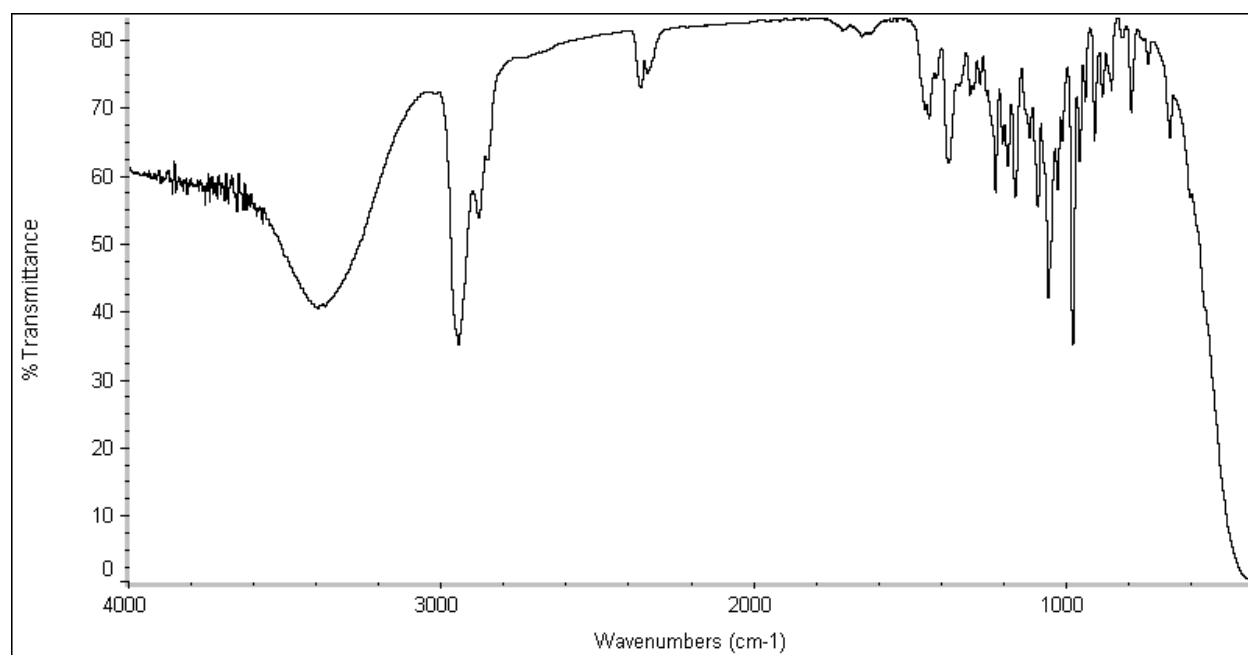
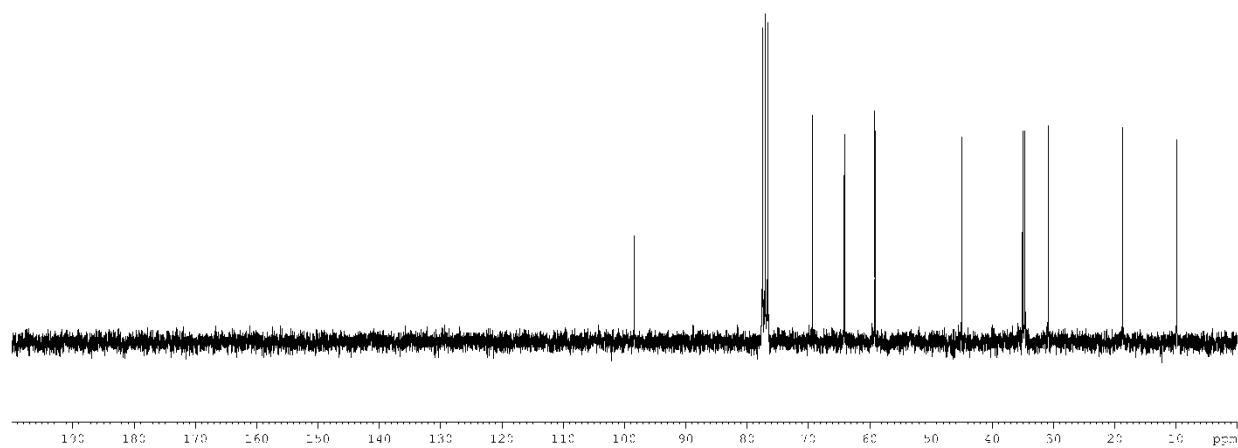
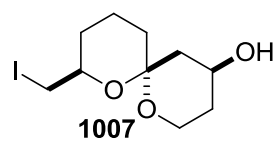


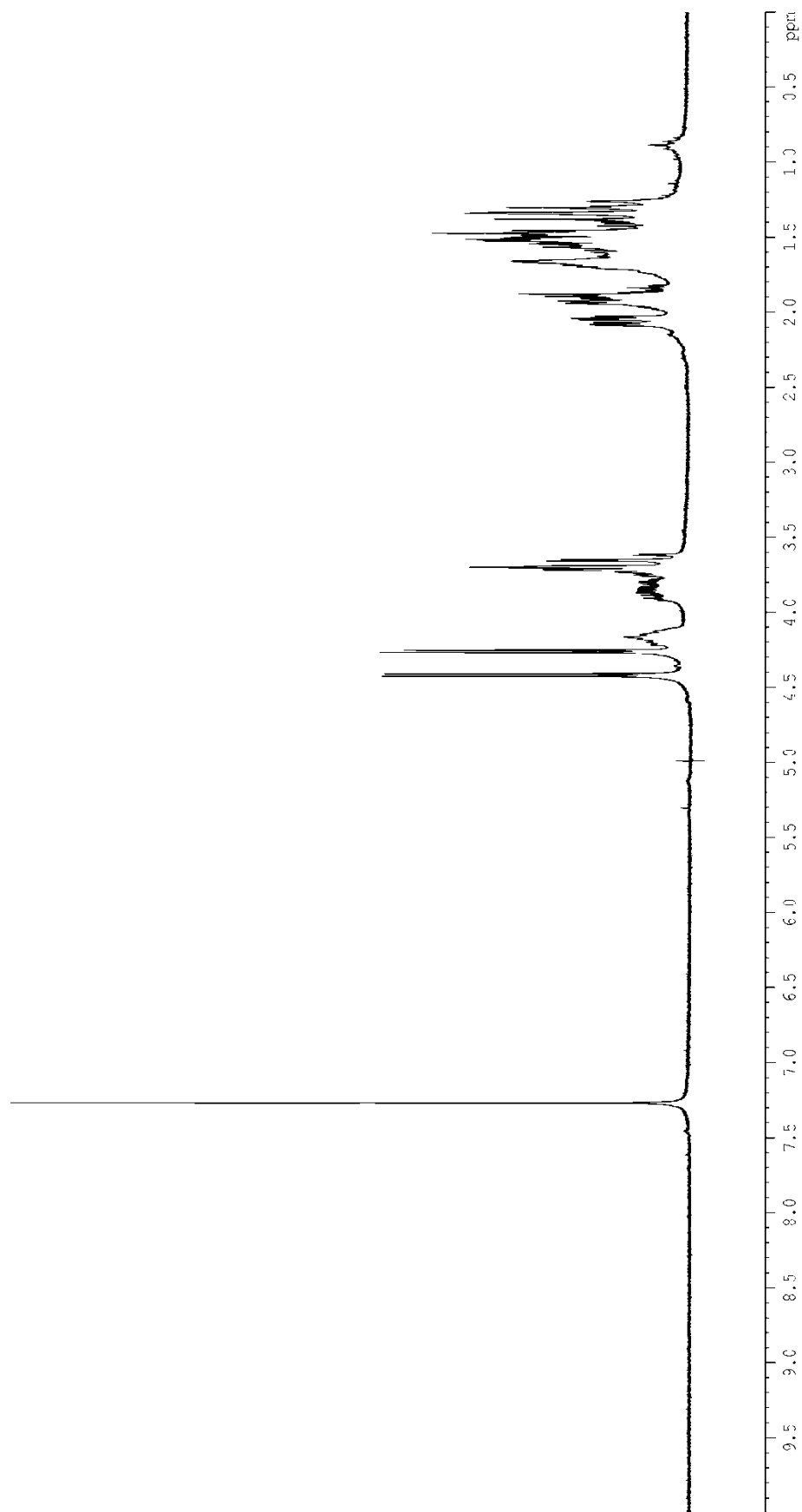
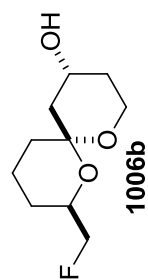


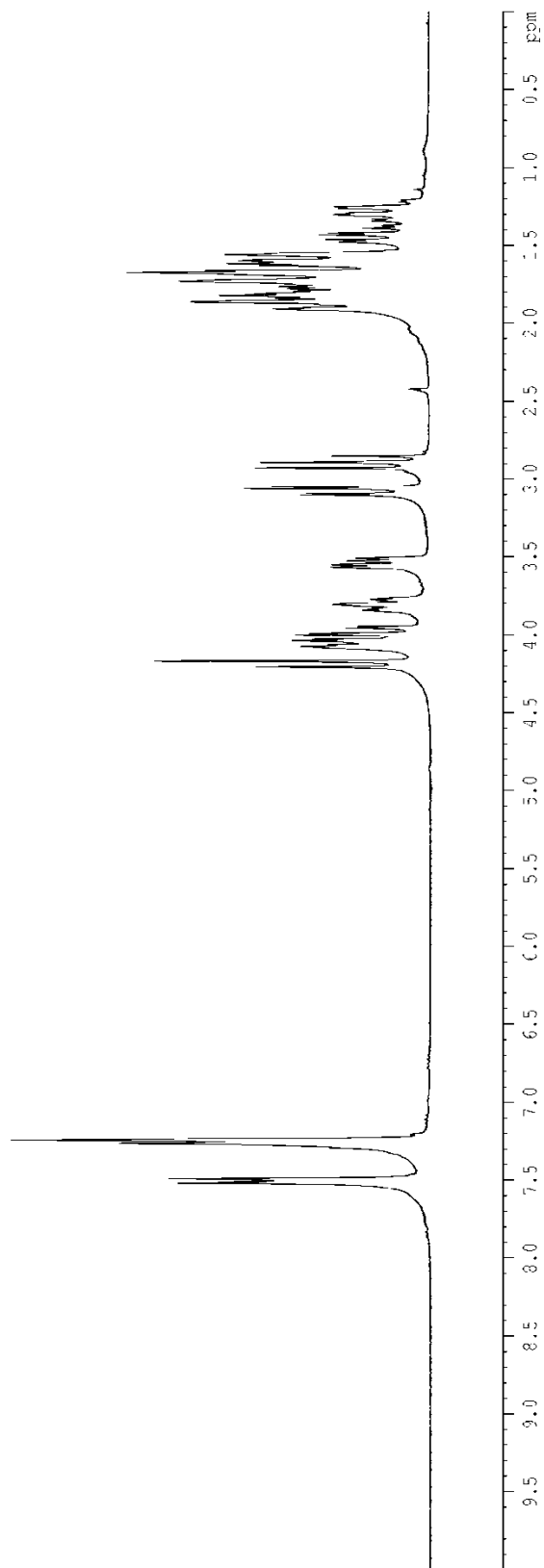
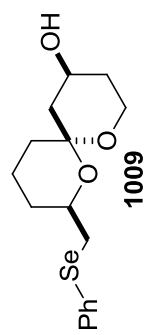


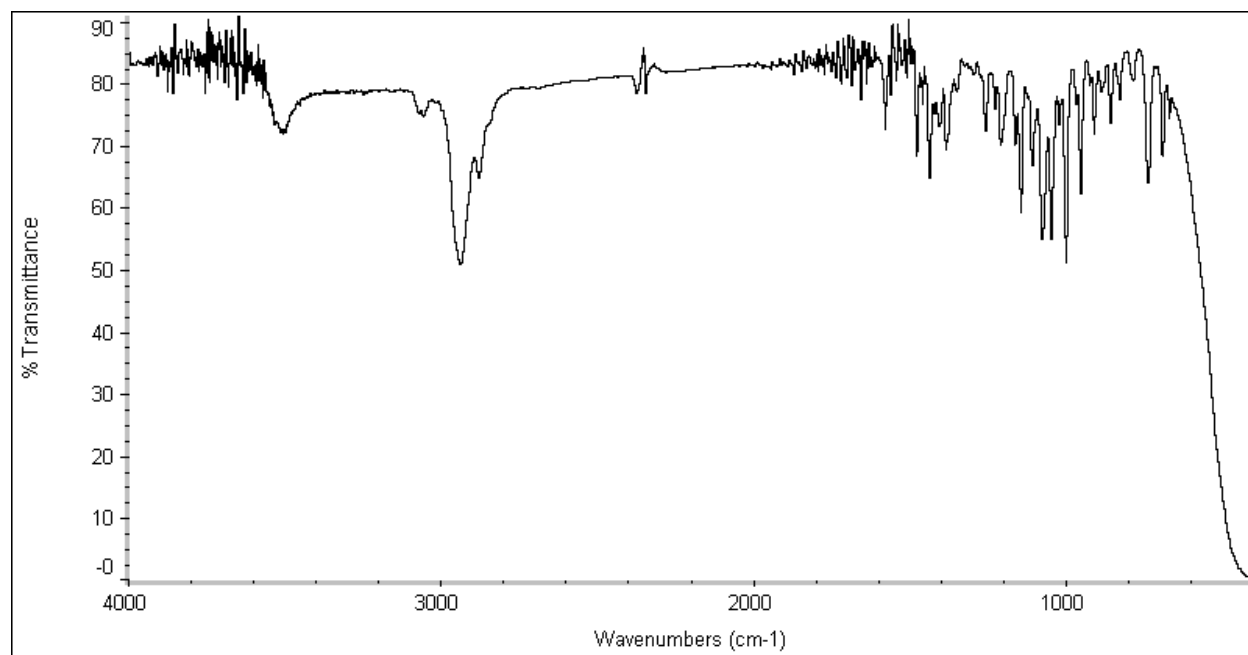
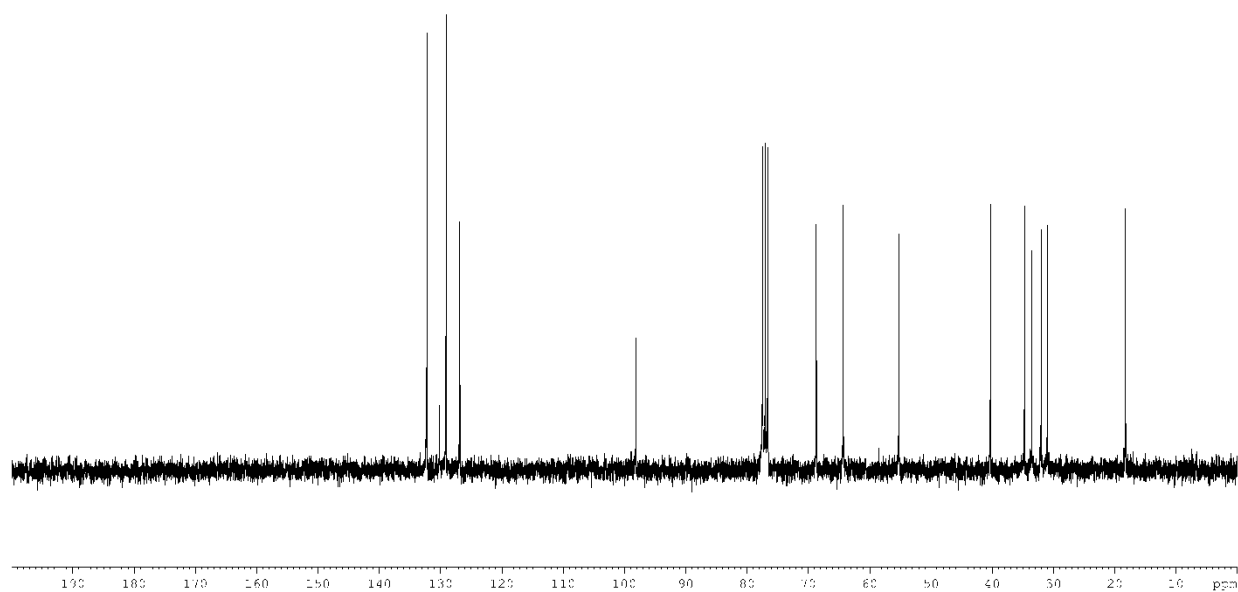


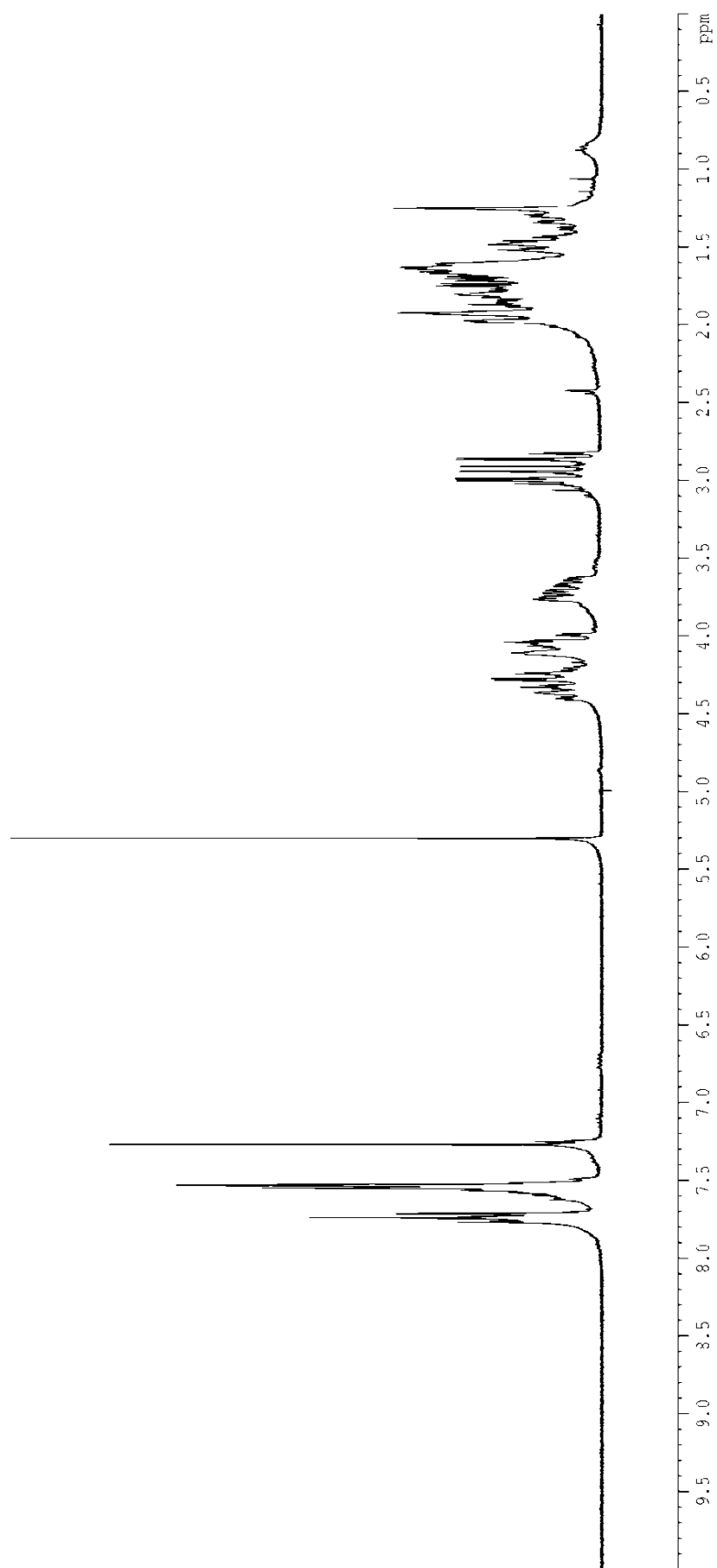
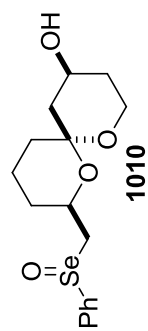












Laura J. Bateman

Education

Ph.D., Syracuse University, (Dec. 2012), 3.69 GPA

Thesis: Nucleophilic Carbon-Carbon Bond Forming Reactions of 2-Methylenetetrahydropyrans

B.S. Chemistry, State University of New York at Oswego, 2005, 3.94 GPA (*Summa cum laude*)

Teaching Experience

- General Chemistry Laboratory Instructor, Siena College and Albany College of Pharmacy and Health Sciences (Fall 2012 – Spring 2013)
 - Created lectures, supervised students during experiments, and graded lab reports
- Organic Chemistry Laboratory Instructor, Albany College of Pharmacy and Health Sciences (Summer 2012)
 - Created lectures and supervised students during laboratory experiments
 - Graded laboratory reports and quizzes to assess student success
- Visiting Assistant Professor of Chemistry, Siena College (August 2011-May 2012)
 - Organic Chemistry Instructor
 - Performed lectures on organic chemistry topics, encouraging mechanism-based learning
 - Fostered undergraduate understanding by holding weekly review sessions
 - Assessed student grades based on exams, online homework, and laboratory performance
 - General Chemistry Instructor
 - Created and taught lectures based on student problem-solving
 - Led recitation sections
 - Evaluated student grades through exams, quizzes, homework, and lab performance
 - Organic Chemistry Laboratory Instructor
 - Created laboratory experiments that extend the students' knowledge from lecture
 - Supervised and assisted students during laboratory experiments, emphasizing proper laboratory techniques and safety while developing their problem-solving skills
 - Oversaw tasks of undergraduate teaching assistants
 - Designed and graded quizzes and lab reports
- Instructor for Organic Chemistry I and II, Syracuse University (May 2011-Aug. 2011)
 - Developed a course of laboratory experiments for summer students
 - Lectured students on subjects of organic chemistry and laboratory techniques
 - Managed graduate teaching assistant duties
 - Assessed student grades based on reports, quizzes, and laboratory performance
- Teaching Assistant, Syracuse University (2005-2011)
Recitation Instructor, Organic and General Chemistry

- Developed question-centered lessons designed to create student involvement
- Aided lecture professors in developing, proctoring, and grading exams
- Graded homework assignments and quizzes

Laboratory Instructor, Organic and General Chemistry

- Created lectures and supervised students during laboratory experiments
- Graded laboratory reports and quizzes to assess student success

- Teaching Assistant for Physical Chemistry Lab I and II, SUNY Oswego, (2004-2005)
 - Assisted Prof. Martha Bruch by providing instruction related to a physical chemistry course, including subjects such as thermodynamics, kinetics, and quantum mechanics
 - Aided students in running NMR experiments, and prepared and restocked chemicals for student use
- Directly supervised 8 undergraduate students with their individual research projects (2006-2012)
 - Guided undergraduate through self-directed bio-diesel synthesis project
 - Demonstrated proper laboratory techniques and encouraged independent problem solving
 - Taught undergraduates to use various instruments

Research Experience

- Research Assistant, Syracuse University (2006-2011)
 - Mentored by Prof. Nancy I. Totah, Organic Chemistry
 - Developed a new carbon-carbon bond forming reaction utilizing a three component coupling methodology
 - Demonstrated selective carbon bond formation in a new carbonyl-ene reaction
 - Designed a bi-directional approach, using subsequent carbonyl-ene reactions, to form bis- β -hydroxy pyrans
- Research Assistant, State University of New York at Oswego (2004-2005)
 - Advised by Prof. Joseph Lefevre, Organic Chemistry
 - Extracted and purified organic compounds found in the bark of native trees
 - Research Assistant, Syracuse University REU program (2004)
 - Mentored by Prof. Michael Sponsler, Organometallic Chemistry
 - Synthesized organic liquid crystals and prepared holographic cells for darkroom use

Presentations

- Bidirectional synthesis of pyranyl diketides via carbonyl-ene reactions of 2-methylene tetrahydropyrans. Bateman, L. J.; Totah, N. I. North-east regional meeting of the American Chemical Society, Potsdam, NY, 2010.
- Substituted 2-methylenetetrahydropyrans as coupling partners in the carbonyl-ene reaction. Bateman, L. J.; Totah, N. I. North-east regional meeting of the American Chemical Society, Hartford, CT, 2009.

- Titanium tetrachloride mediated three component coupling of 2-methylene tetrahydropyrans with activated aldehydes and ketones. Bateman, L. J.; Totah, N. I. Academic Excellence Symposium, Syracuse University, 2007.

Publications

- Gouhua, Liang, Bateman, L. J., Totah, N. I. New reactions of 2-methylenetetrahydropyrans. A three component coupling protocol for the synthesis of tetrahydropyranyl ketides. *Chem. Commun.* **2009**, 42, 6457-6459.

References

Available upon request